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Interferon after surgery for women with advanced (Stage II-IV) epithelial ovarian cancer (Review)

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[Intervention Review]

Interferon after surgery for women with advanced (Stage II-IV) epithelial ovarian cancer

Aramide O Lawal[1], Alfred Musekiwa[1,2], Liesl Grobler[1]

[1]Centre for Evidence-based Health Care, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa. [2]Centre for Evidence-based Health Care, Division of Epidemiology and Biostatistics, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

Contact: Aramide O Lawal, Centre for Evidence-based Health Care, Faculty of Medicine and Health Sciences, Stellenbosch University, PO Box 19063, Tygerberg, Cape Town, Western Cape, 7505, South Africa. aramide0319@yahoo.com.

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ABSTRACT

Background

Epithelial ovarian cancer (EOC) is a life-threatening disease. Most often women become symptomatic only in the advanced stages of the disease, increasing the difficulty of treatment. Whilst the disease responds well to surgery and chemotherapy, the relapse rate is high. New treatments to prevent disease recurrence or progression, prolong survival, and increase the quality of life are needed.

Objectives

To assess the effectiveness and safety of interferon after surgery in the treatment of advanced (stage II-IV) EOC.

Search methods

The Cochrane Gynaecological Cancer Review Group Specialized Register, Cochrane Central Register of Controlled Trials (CENTRAL) Issue 1, 2012, MEDLINE and EMBASE were searched to January 2012. Handsearching of conference proceedings was also undertaken. Reference lists of reviews and included trials were screened and experts in the field were contacted for additional trials. Clinical trials registers were searched for ongoing trials.

Selection criteria

Randomised controlled trials (RCTs) involving participants with advanced EOC that compared post-operative chemotherapy alone with post-operative interferon therapy in combination with chemotherapy or post-operative chemotherapy followed by interferon or observation alone

Data collection and analysis

Two review authors (AL and AM) independently screened the search results for relevant trials and extracted pre-specified information from each included trial. Data were managed using Review Manager 5.1. Hazard ratios (HR) were calculated for time-to-event outcomes and risk ratios (RR) for dichotomous outcomes, with corresponding 95% confidence intervals (CI).

Main results

Five trials, including 1476 participants, were included in the review. Two trials compared interferon with observation alone and three trials compared interferon plus chemotherapy with chemotherapy alone. A meta-analysis of two trials involving 370 participants found no significant difference in both overall survival (HR 1.14, 95% CI 0.84 to 1.55) and progression free survival (HR 0.99, 95% CI 0.79 to 1.24) between the interferon and observation alone groups in post-surgical women who had undergone first-line chemotherapy for advanced

EOC. One trial with 293 participants found that while no significant difference was observed in incidence of nausea or vomiting between the two treatment groups, significantly more flu-like symptoms (RR 2.25, 95% CI 1.73 to 2.91) and fatigue (RR 1.54, 95% CI 1.27 to 1.88) were reported in the interferon group. For the second comparison, a meta-analysis of two trials comprising 244 participants found that although there was no significant difference in overall survival between the interferon plus chemotherapy and the chemotherapy alone group (HR 1.14, 95% CI 0.74 to 1.76), women in the interferon plus chemotherapy group had worse progression free survival than those in the chemotherapy alone group (HR 1.43, 95% CI 1.02 to 2.00). Compared to chemotherapy alone, adding interferon to chemotherapy did not alter the incidence of adverse events in post-surgical women with advanced EOC.

Authors' conclusions

Implications for practice

Based on low quality evidence, the addition of interferon to first-line chemotherapy did not alter the overall survival in post-surgical women with advanced EOC compared with chemotherapy alone. There is low quality evidence to suggest that interferon in combination with chemotherapy worsened the progression free survival in post-surgical women with advanced EOC compared with chemotherapy alone. There is not enough evidence that interferon therapy alone alters overall survival or progression free survival compared to observation alone in post-surgical women who have undergone first-line chemotherapy.

Implications for research

Three of the five trials included in this review were stopped early and were, therefore, underpowered to detect any true effect of the intervention. The trials did not report the results of important outcomes in a uniform manner, preventing statistical aggregation of the results. Trial methodology was poorly reported resulting in unclear risk of bias. For clear recommendations to be made regarding the effectiveness of interferon in the treatment of advanced EOC, long-term, well conducted and adequately powered RCTs would be needed. However, the available data do not suggest that interferon has an adequately advantageous effect to warrant further investigation.

PLAIN LANGUAGE SUMMARY

Interferon therapy after surgery in women with advanced epithelial ovarian cancer

Epithelial ovarian cancer (EOC) is a potentially life-threatening condition. EOC usually develops in women above 50 years of age and is rarely seen in women younger than 35 years old. Early symptoms of the disease are usually mild and vague, making this disease difficult to detect at an early stage. Patients with EOC are relatively asymptomatic until the disease has progressed to an advanced stage.

Although EOC initially responds well to surgery and chemotherapy, there is a high rate of recurrence within 12 to 24 months of treatment. Interferons are proteins that are made and released by host cells in response to the presence of pathogens. They are named after their ability to 'interfere' with viral replication within host cells. Interferon serves two important functions. It signals neighbouring cells and triggers their resistance mechanisms; and it activates other immune cells that kill invading pathogens. This review assessed the effectiveness of interferon therapy in reducing the rate of recurrence or prolonging the time between chemotherapy and subsequent recurrence of the disease.

Five trials, including 1476 participants, were included in the review. Three of the five trials were stopped early. The risk of bias of most of the trials was high or unclear due to incomplete reporting of methods and results. Most of the trials were not large enough to detect any true effect of the intervention. Trials either did not report the results of important outcomes or the results of important outcomes were not uniform between the trials.

The evidence from the three trials suggested that the addition of interferon to first-line chemotherapy did not alter the overall survival in post-surgical women with advanced EOC compared with chemotherapy alone. On the contrary, there is evidence that interferon in combination with chemotherapy worsened progression free survival in post-surgical women with advanced EOC compared with chemotherapy alone. Furthermore, there is not enough evidence that interferon therapy alone improves overall survival or progression free survival in post-surgical women who have undergone first-line chemotherapy when compared with observation alone.

Summary of findings for the main comparison. Interferon + chemotherapy versus chemotherapy alone for women with advanced (Stage II-IV) epithelial ovarian cancer who have undergone surgery

Interferon + chemotherapy versus chemotherapy alone for women with advanced (Stage II-IV) epithelial ovarian cancer who have undergone surgery

Patient or population: Women with advanced (Stage II-IV) epithelial ovarian cancer who have undergone surgery
Settings: Secondary care settings
Intervention: Interferon + chemotherapy versus chemotherapy alone post-surgery for advanced ovarian surgery

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (trials)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Interferon + Chemotherapy versus Chemotherapy alone				
Overall survival	**Study population**		**HR 1.14** (0.74-1.76)	244 (2 trials)	⊕⊕⊝⊝ low[1,4]	
	318 per 1000	**378 per 1000** (295 to 483)				
	Moderate					
	309 per 1000	**368 per 1000** (287 to 470)				
Progression-free survival	**Study population**		**HR 1.43** (1.02 to 2.00)	244 (2 trials)	⊕⊕⊝⊝ **low**[3,2]	
	607 per 1000	**546 per 1000** (297 to 1000)				
	Moderate					
	603 per 1000	**543 per 1000** (295 to 1000)				
Adverse event (flu-like symptoms)	**Study population**		**RR 6.49** (0.41 to 102.25)	230 (2 trials)	⊕⊕⊝⊝ **low**[1,3]	
	87 per 1000	**564 per 1000** (36 to 1000)				

	Moderate				
	100 per 1000	**649 per 1000** (41 to 1000)			
Adverse event (fatigue)	**Study population**		**RR 1.17** (0.82 to 1.68)	97 (1 study)	⊕⊕⊝⊝ **low**[3,4]
	511 per 1000	**597 per 1000** (419 to 858)			
	Moderate				
	511 per 1000	**598 per 1000** (419 to 858)			
Adverse event (neurotoxicity)	**Study population**		**RR 0.87** (0.57 to 1.33)	230 (2 trials)	⊕⊕⊝⊝ **low**[3, 4]
	270 per 1000	**235 per 1000** (154 to 359)			
	Moderate				
	244 per 1000	**212 per 1000** (139 to 325)			

*The basis for the **assumed risk** (e.g. the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] High risk of bias due to study being stopped early
[2] Significant heterogeneity between the trials
[3] The method of randomisation was not described and allocation concealment was not mentioned
[4] Small sample size, potentially underpowered study

Summary of findings 2. Interferon versus observation alone for women with advanced (Stage II-IV) epithelial ovarian cancer

Interferon versus observation alone for women with advanced (Stage II-IV) epithelial ovarian cancer

Patient or population: women with advanced (Stage II-IV) epithelial ovarian cancer who have undergone surgery
Settings: Secondary care settings
Intervention: Interferon versus observation alone post-surgery for advanced epithelial ovarian cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (trials)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Interferon versus observation alone				
Overall survival	**Study population**		**HR 1.14** (0.84 to 1.55)	370 (2 trials)	⊕⊕⊖⊖[1,3] **low**	
	140 per 1000	**74 per 1000** (35 to 153)				
	Moderate					
	306 per 1000	**178 per 1000** (88 to 329)				
Progression-free survival	**Study population**		**HR 0.99** (0.79 to 1.24)	370 (2 trials)	⊕⊕⊖⊖ **low**[1,2]	
	571 per 1000	**629 per 1000** (429 to 920)				
	Moderate					
	571 per 1000	**628 per 1000** (428 to 919)				
Adverse event (flu-like symptoms)	**Study population**		**RR 2.25** (1.73 to 2.91)	293 (1 study)	⊕⊕⊖⊖ **low**[1,2]	
	315 per 1000	**710 per 1000** (546 to 918)				
	Moderate					
	315 per 1000	**709 per 1000** (545 to 917)				

Adverse event (fatigue)	**Study population**		**RR 1.54** (1.27 to 1.88)	293 (1 study)	⊕⊕⊖⊖ **low**[1,2]
	477 per 1000	**734 per 1000** (605 to 896)			
	Moderate				
	477 per 1000	**735 per 1000** (606 to 897)			
Adverse event (nausea/ vomiting)	**Study population**		**RR 1.21** (0.91 to 1.62)	293 (1 study)	⊕⊕⊖⊖ **low**[1,2]
	349 per 1000	**422 per 1000** (318 to 565)			
	Moderate				
	349 per 1000	**422 per 1000** (318 to 565)			

*The basis for the **assumed risk** (e.g. the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Method of randomisation and allocation concealment were not reported on resulting in a potential high risk of selection bias. Participants were not blinded to the treatment which may have affected the performance of the control group resulting in a potentially high risk of performance bias.
[2] Small sample size, potentially underpowered study
[3] Imprecise effect estimate as evidenced by wide confidence interval.

BACKGROUND

Description of the condition

Worldwide, epithelial ovarian cancer (EOC) is the sixth most common cancer among women. There are more than 200,000 new cases diagnosed each year, accounting for approximately 4% of all cancers diagnosed in women. EOC is less common in women under the age of 35 years, and its incidence increases with age (GLOBOCAN 2002). In Europe, approximately 37% of women with EOC are alive five years after diagnosis (EUROCARE 2003). This is largely because the early stages of the disease often present with very few, if any, specific symptoms so most women present with advanced stage disease (Jemal 2008).

According to the International Federation of Gynecology and Obstetrics (FIGO), ovarian cancer is staged as follows (FIGO nomenclature, Rio de Janeiro 1988).

- Stage I: the cancer is limited to the ovaries.
- Stage II: the cancer involves one or both ovaries with spread to other pelvic organs or surfaces.
- Stage III: the cancer spreads outside the pelvis to the abdominal area, including spread to the liver surface.
- Stage IV: the cancer spreads to the liver or outside the peritoneal cavity to areas such as the chest or brain.

More details are given in Table 1.

Patients with EOC are often relatively asymptomatic until the disease has progressed to an advanced stage. Some early symptoms may include bloating, pelvic or abdominal pain, difficulty eating or feeling full quickly, or a frequent need to urinate. The symptoms are usually mild and often go undetected (Twombly 2007). The five-year survival rates of stage II, III and IV invasive EOC patients are 66%, 34% and 18% respectively (ACS 2013).

Several risk factors for EOC have been identified and include the following: a family history of the disease, refractory infertility or nulliparity (not having borne children), and certain mutations in the BRCA1 and BRCA2 tumour suppressor genes. Multiparity (having given birth two or more times), use of oral contraceptives, and tubal ligation or hysterectomy have been shown to reduce the risk of EOC. Five years of oral contraceptive use by women, including those with a family history of the disease, can reduce their risk of EOC by up to 50% (Holschneider 2000).

Description of the intervention

While EOC responds well to surgery and chemotherapy, trials show that within 12 to 24 months post-surgery and first-line chemotherapy, 80% of patients experience disease recurrence or progression (Sourbier 2012). There is a need to explore new treatments that could prevent disease recurrence or progression after first-line treatment. A recent Cochrane review concluded that there is not sufficient evidence that maintenance chemotherapy is more beneficial than observation alone for advanced EOC (Mei 2010; Mei 2011). Maintenance whole abdominal radiotherapy may improve the five-year progression free survival (PFS) (Pickel 1999; Sorbe 2003; Mei 2011); however, it is rarely recommended because of its severe side effects. Interferons (IFNs) could be potentially useful in the treatment of EOC (Mei 2011).

In the 1980s, interferon-alpha (INFα) was assessed as a maintenance therapy for patients with multiple myeloma (a cancer of the plasma cells in bone marrow). As a single agent, interferon has a low response rate in myeloma patients with responses of approximately 15%. However, in patients who demonstrated no evidence of disease progression following primary chemotherapy, maintenance chemotherapy with low-dose subcutaneous INFα improved progression free and overall survival (Mandelli 1990; Hall 2004). INFα has been shown to have an in vitro activity against EOC cell lines (Epstein 1980; Hall 2004) and a limited clinical benefit in advanced EOC (Freedman 1983; Einhorn 1988; Hall 2004). It can be hypothesized that subcutaneous INFα may act as an effective maintenance therapy in patients with advanced EOC and thus improve overall survival (Hall 2004).

How the intervention might work

Interferons (IFNs) are a family of cytokines that demonstrate antiviral, immunomodulatory and antiproliferative activities. The IFNs are classified as type I (α, β, τ, and ω), II (γ) or III (λ) according to structural homology, cell-surface receptor-binding and functional activity. Type I IFNs are secreted at low levels by almost all cell types. IFNα and IFNβ are used clinically to treat viral infections, such as hepatitis B and C, and to treat certain malignancies such as malignant melanoma, hairy cell leukaemia, Kaposi's sarcoma, chronic myelogenous leukaemia and renal cell carcinoma (Schroder 2004; Maher 2007; Tsuno 2009).

In addition to their structural differences, INFs alpha (α) and gamma (γ) differ in some respects. INFα is known for its ability to make cells resistant to viral infections while INFγ is known for its ability to regulate overall immune system functioning. Also, while INFα is produced by almost every cell in the body, INFγ is produced only by specialised cells in the immune system, known as T lymphocytes and natural killer cells.

INFα is a cytokine with multiple targets and mechanisms of action that are believed to contribute to its well-known anti-tumour activity, including inhibition of cell proliferation, induction of differentiation (cell maturation) or apoptosis (programmed cell death), stimulation of the immune system, and angiostatic activity (prevention of blood vessel growth) (Gresser 2002; Dunn 2006; Gresser 2007; Moserle 2008). INFα has been widely used to treat patients with solid tumours, including EOC, generally with unsatisfactory clinical results (Moserle 2008). Nevertheless, major clinical responses have occasionally been reported in some patients (Berek 1985; Nardi 1990; Willemse 1990; Moserle 2008), prompting the conduct of several large scale clinical trials. The tumour or host features underlying positive and negative outcomes of INFα therapy remain unknown for most cancers (Moserle 2008).

Why it is important to do this review

Due to the lack of sustained response to chemotherapy for the treatment of advanced EOC, there is a need to explore other potential treatment modalities such as the use of INF. This review aimed to assess the effectiveness and safety of interferon in the treatment of advanced (stage II-IV) EOC.

OBJECTIVES

To assess the effectiveness and safety of interferon after surgery in the treatment of advanced (stage II-IV) EOC.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Post-operative patients (adult women aged 18 years and above) with diagnosed Stage II, III (micro or macro) or IV EOC.

Types of interventions

Intervention

Post-operative treatment with interferon alone or interferon combined with other cytotoxic agents. Type I interferons (alpha (α) and beta (β)) and Type II interferons (gamma (γ)) will be included. Some of the commercially available brands of interferon include interferon alfacon-1 (Infergen), interferon-alfa-2a (Roferon-A), pegylated interferon alfa-2a, interferon alfa-n3 (Alferon-N), interferon alfa-2b, pegylated interferon alfa-2b, interferon beta-1a (Avonex), interferon beta-1b (Betaseron), and interferon gamma-1B (Actimmune).

Control

Any post-operative chemotherapy regimen or placebo.

Types of outcome measures

Primary outcomes

1. Overall survival (OS): time (in days) from the date of randomisation until death.

2. Progression free survival (PFS): time (in days) from randomisation to progression of disease or death (whichever occurs first). Disease progression is defined as the appearance of one or more new lesions or unequivocal progress of existing lesions, or both.

Secondary outcomes

1. Quality of life (QoL), measured using a scale that has been validated through reporting of norms in a peer-reviewed publication.

2. Response (number of patients showing complete clinical response) as defined according to internationally agreed criteria (e.g. World Health Organization (WHO)).

3. Adverse events:

- toxicity (flu-like symptoms, fatigue, nausea and vomiting, etc),
- other adverse events (neurological, dyspnoea, depression and anxiety, skin change or rash, alopecia, arthralgia or arthritis, insomnia, haematological, hepatic, other).

Search methods for identification of studies

A comprehensive and exhaustive search of the literature was executed in an attempt to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

Electronic searches

We searched the following databases and trial registers for relevant trials: Cochrane Gynaecological Cancer Review Group Specialized Register; Cochrane Central Register of Controlled Trials (CENTRAL) Issue 1, 2012; MEDLINE and EMBASE to January 2012. All relevant articles found were identified on PubMed and further searches were carried out for newly published articles using the 'related articles' feature.

The MEDLINE, EMBASE and CENTRAL search strategies are presented in Appendix 1.

We searched the reference lists of all included trials for relevant trials. We also contacted authors of included trials and experts in the field of ovarian cancer and gynaecology to identify any additional published or unpublished trials.

Searching other resources

Handsearching

The following sources were handsearched for relevant trials or conference reports and abstracts.

- Gynaecology Oncology (Annual Meeting of the American Society of Gynaecologic Oncologists), from November 1972 to June 2012 (Volume 1 to Volume 125, Issue 3).
- International Journal of Gynaecological Cancer (Annual Meeting of the International Gynaecologic Cancer Society), 1991 to July 2012 (Volume 1 to Volume 22, Issue 6).
- British Journal of Cancer, July 1973 to June 2012 (Volume 28 to 107, Issue 1)

Grey literature

Metaregister, Physicians Data Query, www.controlled-trials.com/rct, www.clinicaltrials.gov, www.cancer.gov/clinicaltrials, and Gynaecology Oncologists of Canada (www.g-o-c.org) were searched for ongoing trials.

Data collection and analysis

Selection of studies

Two review authors, Aramide Lawal (AL) and Alfred Musekiwa (AM), independently screened the results of the search to select potentially relevant trials and applied the eligibility criteria using a pre-designed eligibility form based on the inclusion criteria. Corresponding full text articles were retrieved and used to apply the eligibility criteria. Each of the articles were scrutinized to ensure that multiple publications from the same trial were included only once. Where eligibility was unclear, we sought clarification from the trial authors and re-assessed the corresponding articles. We resolved any differences between the eligibility results by consensus. We excluded trials that did not meet the inclusion criteria and stated the reasons in the 'Characteristics of excluded studies' table.

Data extraction and management

Using a specially designed pre-piloted data extraction form, two review authors (AL and AM) independently extracted information on methods, participants, interventions, and outcomes from each included trial. We extracted the number of participants randomised in each group and the numbers analysed for each

outcome. We included dichotomous and time-to-event outcomes. For each dichotomous outcome we extracted the number of participants experiencing the event in each treatment group. For each time-to-event outcome, we extracted the number of participants experiencing the event, the median (range) survival for each treatment group and, where reported, the hazard ratio with corresponding 95% confidence interval (CI) and Log-rank P value. We used some of these data to estimate the log hazard ratio and its standard error using Parmar's methods (Parmar 1998).

The following information was also extracted: trial author(s), year of publication, country of origin, journal citation (including language), trial setting, trial design and methodology, details of the participants (demographic characteristics, total number enrolled, age, comorbidities, and patient characteristics), criteria for participant inclusion and exclusion, ovarian cancer details at diagnosis (FIGO stage, histological cell type, tumour grade, extent of disease, disease free interval, number of recurrences), interferon details and control or comparison details (route of administration, dosage, duration), duration of follow-up, risk of bias in trial, and details about each of the primary and secondary outcomes. Trial authors were contacted in the case of unclear or missing data. We resolved any disagreements regarding extracted data by consensus.

Assessment of risk of bias in included studies

Two review authors (AL and AM) independently assessed the risk of bias in included studies using the Cochrane Collaboration's tool (Higgins 2011). This included assessment of the following.

- Selection bias:
  - random sequence generation,
  - allocation concealment.
- Performance bias:
  - blinding of participants and personnel (patients and treatment providers).
- Detection bias:
  - blinding of outcome assessment.
- Attrition bias:
  - incomplete outcome data. We recorded the proportion of participants whose outcomes were not reported at the end of the trial. We coded a satisfactory level of loss to follow-up for each outcome as:
    - low risk of bias, if fewer than 20% of patients were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms,
    - high risk of bias, if more than 20% of patients were lost to follow-up or reasons for loss to follow-up differed between treatment arms,
    - unclear risk of bias, if loss to follow-up was not reported.
- Reporting bias:
  - selective reporting of outcomes.
- Other possible sources of bias.

We categorized our judgements as 'yes', 'no', or 'unclear', indicating a low, high, or unclear risk of bias, respectively. The results were summarized using the 'risk of bias summary' and the 'risk of bias graph' in addition to the 'risk of bias tables'. Where necessary, we contacted the trial authors for clarification. We resolved any disagreements regarding risk of bias assessment by consensus.

Measures of treatment effect

We used Review Manager 5.1 (Revman 5) to calculate hazard ratios for time-to-event outcomes and risk ratios for dichotomous outcomes. For time-to-event outcomes, we calculated the log hazard ratios and their corresponding standard errors using Parmar's methods (Parmar 1998). These values were then entered into Revman 5 using the generic inverse variance method of meta-analysis. We presented hazard ratios (HR) and risk ratios (RR) with their corresponding 95% confidence intervals (CI).

Dealing with missing data

Where data from the trial reports were insufficient, unclear or missing, we contacted the trial authors by e-mail for additional information or clarification. We carried out analyses according to the intention-to-treat (ITT) principle where there were no missing data. In the case of missing data, we carried out analyses according to the available case analysis. We did not impute missing outcome data for any of the outcomes.

Assessment of heterogeneity

We assessed statistical heterogeneity by visually inspecting the forest plots to detect overlapping CIs, by estimation of the percentage heterogeneity between trials that cannot be ascribed to sampling variation (Higgins 2003), and also by a formal statistical test of the significance of the heterogeneity (Deeks 2001). We could not carry out subgroup analyses because there were only two trials per meta-analysis. We used the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) for interpreting the heterogeneity results. Where substantial heterogeneity was detected, we did not report the pooled result of the meta-analysis but instead reported results from each trial separately.

Assessment of reporting biases

We could not construct funnel plots to assess the potential for small trial effects, such as publication bias, because we only had two trials per meta-analysis.

Data synthesis

We decided a priori to use the random-effects method irrespective of the results of the tests for heterogeneity. We calculated hazard ratios for time-to-event outcomes and risk ratios (RR) for dichotomous outcomes using Revman 5. Corresponding 95% CIs were also calculated. None of the trials included in the review compared multiple treatment regimes or assessed a continuous outcome.

We compared the effectiveness of interferon versus observation alone as well as interferon in combination with chemotherapy versus chemotherapy alone.

Subgroup analysis and investigation of heterogeneity

The pre-specified subgrouping to investigate for possible sources of heterogeneity across trials was:

- FIGO stage of EOC (II, III, and IV).

Although we had planned to conduct subgroup analyses in the case of statistically significant heterogeneity between trials, this could not be done because there were only two trials per meta-analysis.

Sensitivity analysis

Because of the small number of trials per meta-analysis, we did not perform sensitivity analysis to assess the influence of risk of bias (allocation concealment) on the findings.

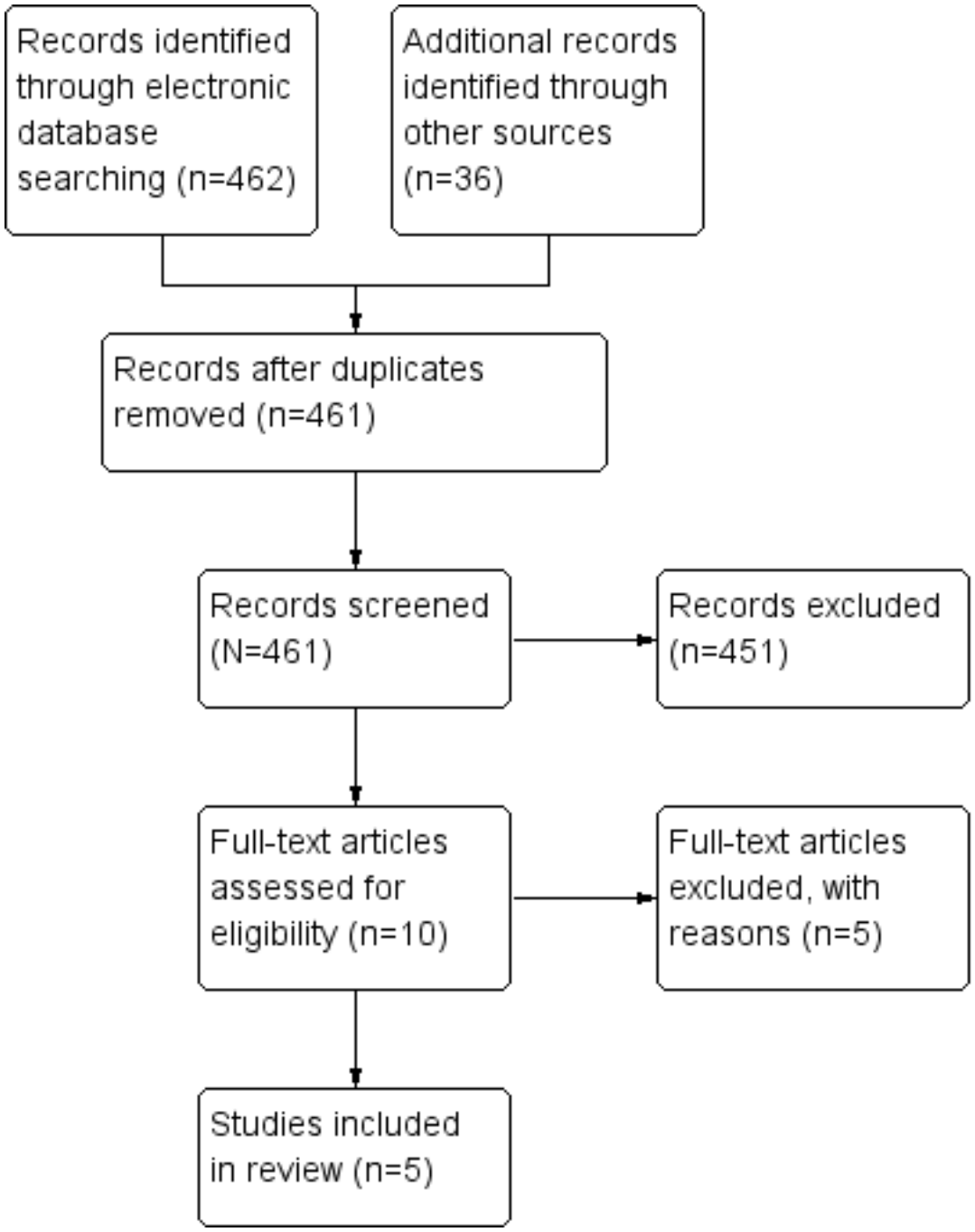
RESULTS

Description of studies

Results of the search

A total of 462 records were obtained from electronic databases and an additional 36 records were identified from other sources (see Figure 1). Following de-duplication of the records a total of 461 records were assessed for eligibility. Ten full text articles were obtained. Five trials were deemed eligible for inclusion in the review. Two trials were excluded from the review; the reasons are set out in the Characteristics of excluded studies table. We were unclear about the eligibility of three trials as we were unable to obtain the full texts of these trials (Kosmidis 1997; Sumrit 1998; Zhyl'chuk 1998). Information on these trials has been included in the Characteristics of studies awaiting classification table.

Figure 1. Study flow diagram.



Included studies

Details of all the included trials are presented in the table Characteristics of included studies. Four of the five trials were multicentre trials (Windbichler 2000; Hall 2004; Alberts 2006; Alberts 2008). The five trials included a total of 1476 randomised participants, and sample sizes ranged from 70 (Alberts 2006) to 847 (Alberts 2008) participants.

Settings

The trials were conducted in the United Kingdom (Hall 2004), Austria (Windbichler 2000), Italy (Bruzzone 1997) and the United States of America (USA) (Alberts 2006). The Alberts 2008 trial enrolled participants from Europe and North and South America. All trials were carried out in a secondary care setting. No trials were reported by primary care physicians or clinics.

Participants

The participants were women with histologically proven, advanced (FIGO stage II-IV) EOC who had undergone debuking surgery. Trials included women with adequate bone marrow, hepatic and renal function. According to the inclusion criteria of this review only participants with FIGO stage II-IV EOC were to be included.

Windbichler 2000, however, enrolled participant with FIGO Stage Ic-IV EOC and 11% of the included participants were classified as having FIGO Stage Ic EOC. The results of this trial were not analysed by the FIGO stage of the participants, so we were unable to tease out the information pertinent to our review. We did not feel justified in excluding this trial since only 11% of the participants had FIGO Stage Ic EOC, hence this trial was included. Alberts 2008 included a majority of participants with FIGO Stage III EOC, with 76.5% and 76.7% in the experimental and comparison groups respectively. The percentage of women with Stage IV EOC was 23.5% and 23.3% respectively. Alberts 2006 did not report on the FIGO staging of the participants. Windbichler 2000 stated that the percentage of women with FIGO Ic, II, III and IV EOC in the interferon group were 11%, 14%, 74% and 1% respectively, whilst the percentages in the chemotherapy group were 16%, 9%, 69% and 6% respectively. Hall 2004 reported that the percentages of women with FIGO Stage I, II, III and IV EOC in the interferon group were 7%, 22%, 63% and 15%, whereas in the chemotherapy group the percentages were 8%, 13%, 64% and 15% respectively. Bruzzone 1997 reported the percentages of women with FIGO I/II, III, IV EOC in the intervention group to be 4%, 83% and 13%, and in the control group 86% of women had FIGO stage III and 14% had stage IV disease.

Windbichler 2000 included women aged less than 75 years and excluded those with severe cardiovascular disease, life expectancy less than three months, recent malignancy or thromboembolic disease. Bruzzone 1997 enrolled women aged between 18 and 75 years and excluded those with extra-abdominal localisation of disease (Stage IV) and previous malignancies. Hall 2004 enrolled women with no evidence of disease progression after post-operative chemotherapy. Alberts 2006 included women with not more than 120 days between chemotherapy and second-look surgery who had a patent intraperitoneal space at the time of second-look surgery. Alberts 2008 enrolled previously untreated histologically diagnosed women following the initial surgery and who were randomised within 12 weeks after that surgery.

Intervention

The trials investigated the effectiveness of interferon with or without chemotherapy, either as part of the first-line therapy following surgery (Bruzzone 1997; Windbichler 2000; Alberts 2008) or as a form of maintenance therapy following surgery and first-line chemotherapy (Hall 2004; Alberts 2006).

Two forms of interferon were investigated, INFα (Bruzzone 1997; Hall 2004; Alberts 2006) and INFγ (Windbichler 2000; Alberts 2008). The interferon therapy was administered subcutaneously in two trials (Hall 2004; Alberts 2008) and intraperitoneally in three trials (Bruzzone 1997; Windbichler 2000; Alberts 2006).

The chemotherapy received by the women, either in conjunction with the interferon therapy or prior to interferon therapy, also differed between trials (see the details outlined in the table Characteristics of included studies).

The duration of treatment with interferon therapy varied from four years and four months (Bruzzone 1997) to 11 years (Alberts 2006). Duration of treatment was not specified in Alberts 2008.

The control groups received chemotherapy only or observation only. In both Alberts 2006 and Hall 2004 the control group received chemotherapy after surgery and was then observed while the intervention group received interferon. In Windbichler 2000 the control group received cisplatin (100 mg/m^2) and cyclophosphamide (600 mg/m^2) every four weeks for six cycles, that is 24 weeks, and in Bruzzone 1997 the control group received three courses of carboplatin (400 mg/m^2) every 28 days for three weeks. In Alberts 2008 the control group received chemotherapy, which included paclitaxel (175 mg/m^2) over 3 hrs followed by carboplatin every three weeks continously. A total of six cycles were given unless disease progression or dose-limiting toxicity occurred, or patients refused further treatment.

Outcomes

Primary outcomes including overall survival were reported by all included trials. Progression free survival was reported by Bruzzone 1997, Hall 2004, Alberts 2008 and Windbichler 2000. Treatment failure free survival was, however, only reported by Alberts 2008.

Secondary outcomes including adverse events were reported in three trials (Hall 2004; Alberts 2006; Alberts 2008). Response outcomes were reported by Windbichler 2000 and toxicity was reported by Windbichler 2000, Hall 2004 and Bruzzone 1997.

Excluded studies

Two trials were excluded because they were not randomised controlled trials but controlled clinical trials (Cardamakis 1999; Berek 2000). One trial (Kosmidis 1997) did not contain sufficient data for analysis because the outcomes that were measured and reported on were not relevant to our review. We have requested additional information from the authors, but we have not yet received a response. This study in addition to two further trials are awaiting classification because full text articles could not be found even after extensive searching and contacting the authors of the respective papers (Sumrit 1998; Zhyl'chuk 1998).

Risk of bias in included studies

Summaries of the risk of bias across included trials are provided in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included trials.

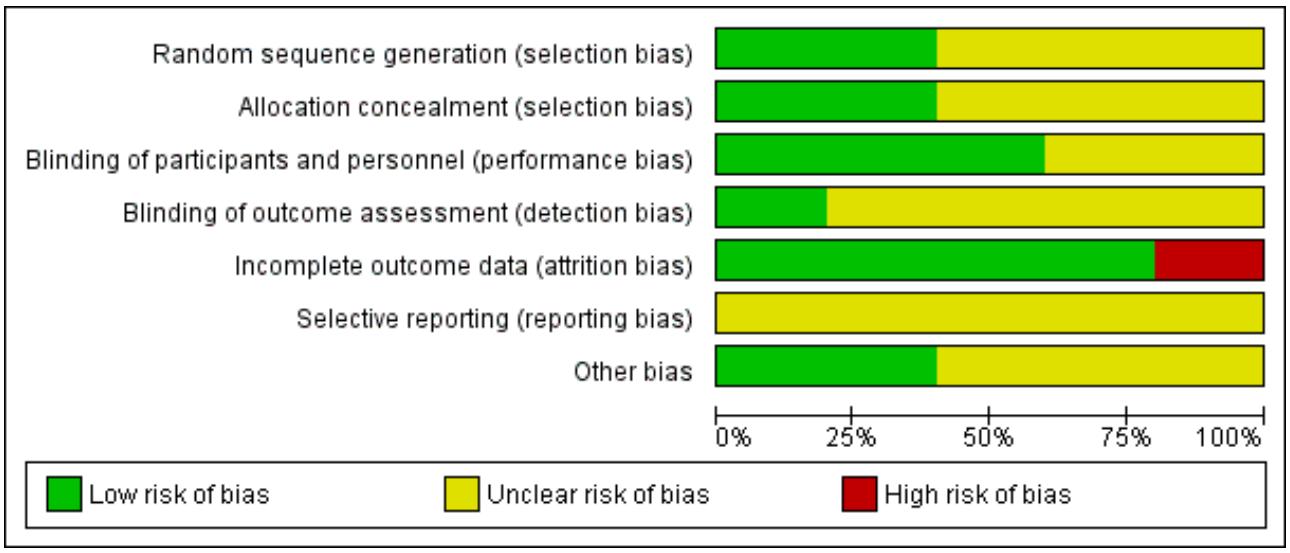
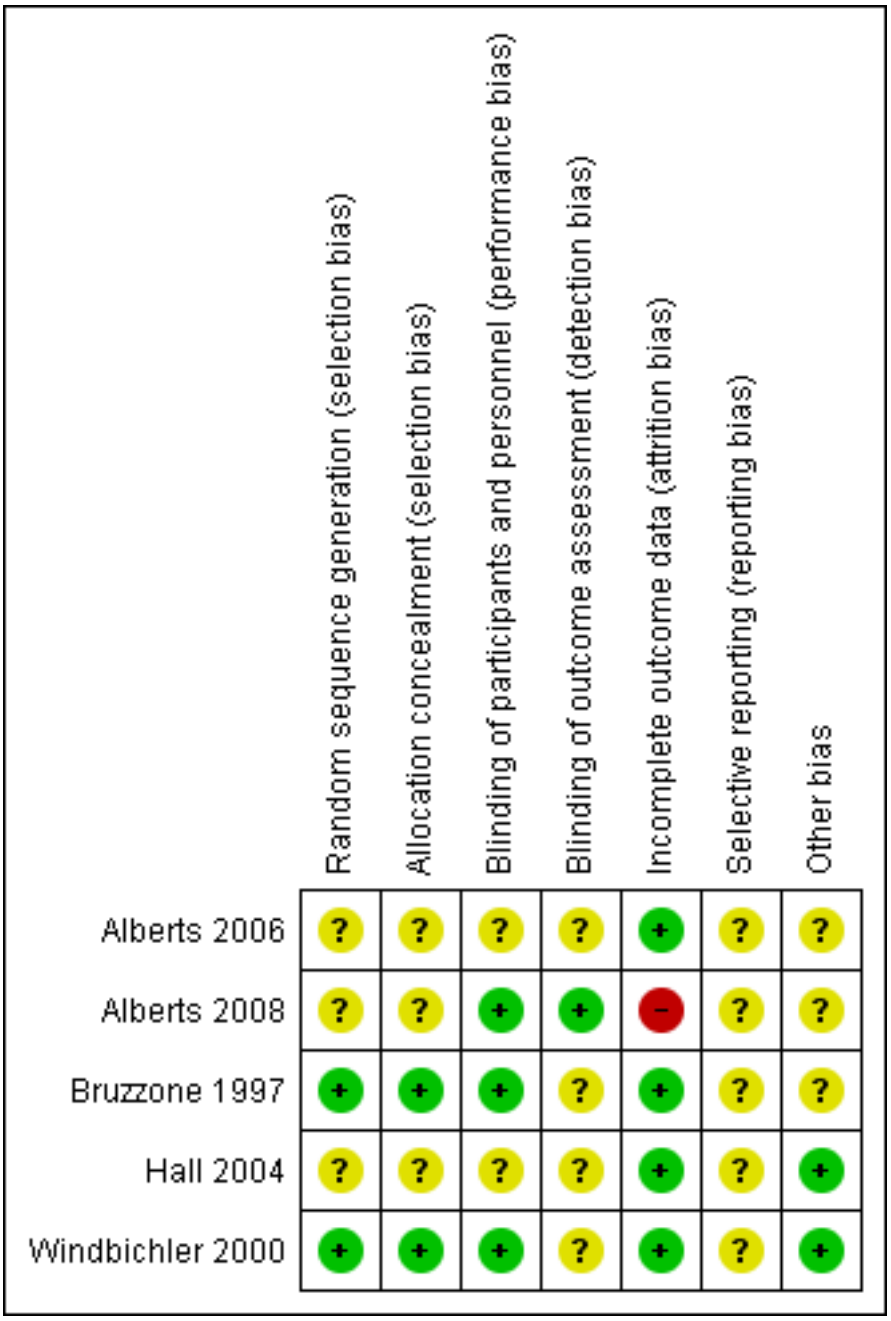


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Bias related to randomisation was judged to be low in two trials (Bruzzone 1997; Windbichler 2000) and unclear in the remaining three (Hall 2004; Alberts 2006; Alberts 2008). Windbichler 2000 had computer generated randomised lists and Bruzzone 1997 used random number tables and specific lists of randomisation lists in blocks of varying sizes. The remaining trials were unclear and we have requested clarification from authors and are awaiting their responses.

Blinding

Where blinding of participants was not reported on, or not described, we judged the trial to be at unclear risk when the control participants did not receive any treatment (Hall 2004; Alberts 2006). Where blinding of participants was not reported on but the control group received chemotherapy alone we judged the risk of bias to be of unclear (Bruzzone 1997; Windbichler 2000; Alberts 2008). Adequate blinding of outcome assessors was described in Alberts 2008. Blinding of outcome assessors was not described in any of the other trials and the bias was therefore judged as unclear risk of bias (Bruzzone 1997; Windbichler 2000; Hall 2004; Alberts 2006).

Incomplete outcome data

The risk of bias due to attrition was judged to be low in three of the five included trials. Five out of 57 people were lost to follow-up in the intervention group as well as the same proportion in the control group in one trial (Bruzzone 1997), and at least 96% received the intervention in another trial (Hall 2004). In one trial (Alberts 2008) the incidence of withdrawal was 24% and 17% in the intervention and control groups respectively, and another trial recorded 9% and 10% withdrawals due to disease progression in the intervention and control groups respectively (Windbichler 2000). Alberts 2006 recorded 8% loss to follow-up in the intervention group and none in the control group.

Selective reporting

None of the trial protocols were obtained. Therefore, the risk of bias was judged as unclear for all of the included trials.

Other potential sources of bias

Three of the included trials were stopped early and were therefore judged to have unclear risk of bias. Two of these trials were stopped early due to poor accrual of participants (Bruzzone 1997; Alberts 2006) and the other trial was stopped early based on a decision made by the Data and Safety Monitoring Board (Alberts 2008).

Effects of interventions

See: **Summary of findings for the main comparison** Interferon + chemotherapy versus chemotherapy alone for women with advanced (Stage II-IV) epithelial ovarian cancer who have undergone surgery; **Summary of findings 2** Interferon versus observation alone for women with advanced (Stage II-IV) epithelial ovarian cancer

Interferon versus observation alone

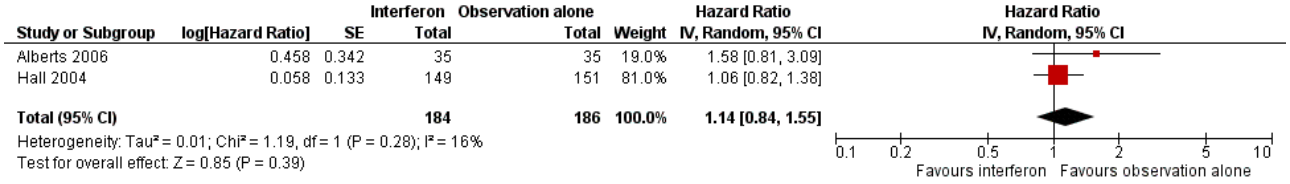
Two trials assessed the effect of interferon versus observation alone (Hall 2004; Alberts 2006).

Primary outcomes

1. Overall survival (OS)

Meta-analysis of the two trials, assessing 370 women, found no significant difference in overall survival between the interferon and observation alone groups (HR 1.14, 95% CI 0.84 to 1.55, Figure 4, Analysis 1.1). The percentage of the variability in effect estimates that was due to heterogeneity rather than chance might not be important (I^2 = 16%).

Figure 4. Forest plot of comparison: 1 Interferon versus observation alone, outcome: 1.1 Overall survival.



2. Progression free survival (PFS)

Meta-analysis of the two trials, assessing 370 women, found no significant difference in progression free survival between the interferon and observation alone groups (HR 0.99, 95% CI 0.79 to 1.24, Analysis 1.2). The percentage of the variability in effect estimates that was due to heterogeneity rather than chance might not be important (I^2 = 0%). Hall 2004 followed up patients for two years (15%, 63%, 14% and 7% of women had stage FIGO Stage I, II, III and IV EOC respectively). The period of follow-up was not stated in Alberts 2006 and 64%, 26% and 10% of the women had FIGO Stage III, II and I EOC respectively.

Secondary outcomes

1. Quality of life (QoL)

This outcome was not reported by the two trials assessing this comparison.

2. Response

This was defined by the number of women with a complete clinical response.

This outcome was not reported by the two trials assessing this comparison.

3. Adverse events

- Toxicity (flu-like symptoms, fatigue, nausea and vomiting, etc)

Alberts 2006 reported toxicity adverse events only for the interferon arm and not for the observation alone arm.

Hall 2004, assessing 293 women, reported significantly more flu-like symptoms (RR 2.25, 95% CI 1.73 to 2.91, Analysis 1.3) and fatigue (RR 1.54, 95% CI 1.27 to 1.88, Analysis 1.4) in the interferon group compared to the observation alone group, but there was no significant difference in the number of women experiencing nausea or vomiting between the two treatment groups (RR 1.21, 95% CI 0.91 to 1.62, Analysis 1.5).

- Other adverse events (neurological, dyspnoea, depression and anxiety, skin change or rash, alopecia, arthralgia or arthritis, insomnia, haematological, hepatic, other)

Both trials (Hall 2004; Alberts 2006) reported other adverse events only for the interferon group and not for the observation alone group.

Interferon + chemotherapy versus chemotherapy alone

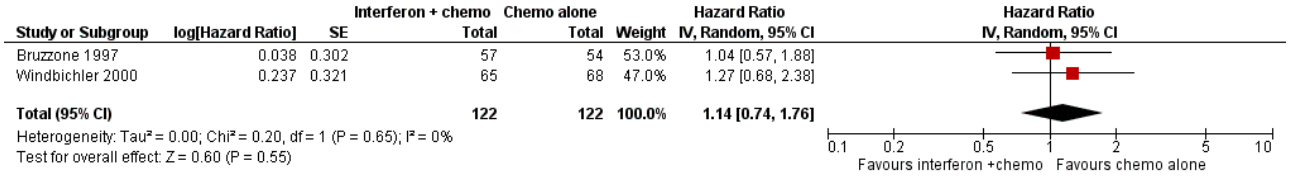
Three trials compared the effect of interferon therapy in combination with chemotherapy versus chemotherapy alone (Bruzzone 1997; Windbichler 2000; Alberts 2008).

Primary outcomes

1. Overall survival (OS)

Meta-analysis of two trials (Bruzzone 1997; Windbichler 2000), assessing 244 women, found no significant difference in overall survival between the interferon plus chemotherapy and the chemotherapy alone groups (HR 1.14, 95% CI 0.74 to 1.76, Figure 5, Analysis 2.1). The percentage of the variability in effect estimates that was due to heterogeneity rather than chance might not be important (I^2 = 0%). The remaining trial (Alberts 2008) could not be included in the meta-analysis because it failed to report the hazard ratio for EOC patients separately, orsufficient information to enable the calculation of the hazard ratio.

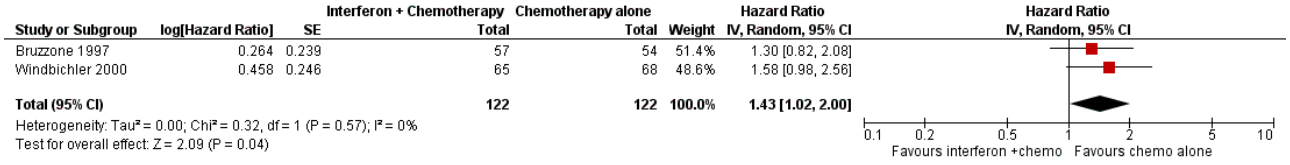
Figure 5. Forest plot of comparison: 2 Interferon + chemotherapy versus chemotherapy alone, outcome: 2.1 Overall survival.



2. Progression *f*ree survival (PFS)

Meta-analysis of two trials (Bruzzone 1997; Windbichler 2000), assessing 244 participants, found that women in the interferon plus chemotherapy group had a higher risk of disease progression compared to the chemotherapy alone group (HR 1.43, 95% CI 1.02 to 2.00, Figure 6, Analysis 2.2). The percentage of the variability in effect estimates that was due to heterogeneity rather than chance might not be important (I^2 = 0%). The remaining trial (Alberts 2008) could not be included in the meta-analysis because it failed to report the hazard ratio for EOC patients separately, or sufficient information to enable the calculation of the hazard ratio.

Figure 6. Forest plot of comparison: 2 Interferon + chemotherapy versus chemotherapy alone, outcome: 2.2 Progression free survival.



Secondary outcomes

1. Quality of life (QoL)

This outcome was not reported by any of the three trials assessing this comparison.

2. Response

One trial (Windbichler 2000), assessing 81 participants, found no significant difference in the number of women with a complete clinical response between the two treatment groups (RR 1.23, 95% CI 0.87 to 1.73, Analysis 2.3).

This outcome was not reported by the other two trials assessing this comparison.

3. Adverse events

Alberts 2008 did not report adverse event results for each arm of EOC patients separately, or any relative measure for the two groups.

- Toxicity (flu-like symptoms, fatigue, nausea and vomiting, etc)

Flu-like symptoms

One trial (Windbichler 2000), assessing 133 participants, found that treatment with interferon plus chemotherapy significantly increased the risk of flu-like symptoms compared to chemotherapy alone (RR 23.54, 95% CI 5.95 to 93.09, Analysis 2.4). Another trial (Bruzzone 1997), assessing 97 participants, found no significant difference in the risk of flu-like symptoms between the two treatment groups (RR 2.00, 95% CI 0.95 to 4.19, Analysis 2.4). These two trials were not pooled in a meta-analysis because of high heterogeneity.

Fatigue

One trial (Bruzzone 1997), assessing 97 participants, found no significant difference in the number of women experiencing fatigue between the two treatment groups (RR 1.18, 95% CI 0.82 to 1.68, Analysis 2.5). Windbichler 2000 did not report on fatigue.

Neither Bruzzone 1997 nor Windbichler 2000 reported on nausea or vomiting.

- Other adverse events (neurological, dyspnoea, depression and anxiety, skin change or rash, alopecia, arthralgia or arthritis, insomnia, haematological, hepatic, other)

The following adverse events were reported by both Bruzzone 1997 and Windbichler 2000. The numbers used in the calculations of treatment effects were derived from the percentages reported.

Neurotoxicity

A meta-analysis of results from Bruzzone 1997 and Windbichler 2000, assessing 230 participants, found no significant difference in

the incidence of neurotoxicity between the two treatment groups (RR 0.87, 95% CI 0.57 to 1.33, Analysis 2.6). The percentage of the variability in effect estimates that was due to heterogeneity rather than chance might not be important (I^2 = 0%).

Alopecia

A meta-analysis of results from Bruzzone 1997 and Windbichler 2000, assessing 230 participants, found no significant difference in the incidence of alopecia between the two treatment groups (RR 0.96, 95% CI 0.74 to 1.23, Analysis 2.7). The percentage of the variability in effect estimates that was due to heterogeneity rather than chance might not be important (I^2 = 0%).

Anaemia

A meta-analysis of results from Bruzzone 1997 and Windbichler 2000, assessing 230 participants, found no significant difference in the incidence of anaemia between the two treatment groups (RR 1.13, 95% CI 0.83 to 1.55, Analysis 2.8). The percentage of the variability in effect estimates that was due to heterogeneity rather than chance might not be important (I^2 = 0%).

DISCUSSION

Summary of main results

Five trials, with a total of 1476 women, were included in the review. Two trials assessed the effectiveness of interferon therapy compared with observation alone in post-surgical women who had undergone first-line chemotherapy for advanced EOC (Hall 2004; Alberts 2006). Three trials investigated the effectiveness of adding interferon to first-line chemotherapy compared to chemotherapy alone in post-surgical women with advanced EOC (Bruzzone 1997; Windbichler 2000; Alberts 2008).

A meta-analysis of two trials (Hall 2004; Alberts 2006) found no significant difference in both overall survival and progression free survival between the interferon and observation alone groups in post-surgical women who have undergone first-line chemotherapy for advanced EOC.

One trial (Hall 2004) found that while no significant difference was observed in the number of women experiencing nausea or vomiting between the two treatment groups, significantly more flu-like symptoms and fatigue were reported in the interferon group compared to the observation group.

A meta-analysis of two trials (Bruzzone 1997; Windbichler 2000) found no significant difference in overall survival between the interferon plus chemotherapy and chemotherapy alone groups in post-surgical women with advanced epithelial ovarian cancer. However, meta-analysis of the same two trials found that women in the interferon plus chemotherapy group had a higher risk of disease progression compared to the chemotherapy alone group.

Based on the results of a meta-analysis of two trials (Bruzzone 1997; Windbichler 2000), the addition of interferon to first-line chemotherapy did not significantly increase the incidence of neurotoxic events, alopecia or anaemia compared to chemotherapy alone. While Windbichler 2000 reported a significant increase in flu-like symptoms in the interferon and chemotherapy group compared to the chemotherapy alone group, Bruzzone 1997 reported no significant difference between the two groups for the incidence of flu-like symptoms or fatigue.

It is also important to note that three of the five included trials were stopped early. Bruzzone 1997 was stopped early due to toxicities and the higher costs in the interferon arm, considering the absence of a clinically important survival advantage. Alberts 2006 was stopped early due to poor accrual of participants. Alberts 2008 was stopped early following a protocol-defined second interim analysis, which revealed a significantly shorter overall survival time in women receiving interferon with chemotherapy compared to chemotherapy alone. Stopping a trial early may result in the study being underpowered to detect a true effect if the effect size is small.

Overall completeness and applicability of evidence

A substantial amount of information on important outcomes has been requested from the trial authors, but has not yet been received. Four of the five included trials were conducted in developed countries. In one trial women were recruited from countries in Europe and North and South America, thus making the findings somewhat more applicable to developed and developing countries. In undeveloped settings, the cost implications of interferon therapy versus the effectiveness of the treatment would have to be considered more closely. There were no trials completed within the last three years that met the inclusion criteria of the review. There remains a possibility that interferon therapy is more effective with some of the newer chemotherapy regimes, but this has not been tested. Most of the included trials failed to measure or report on important secondary outcomes such as clinical response, quality of life or the cost implications of interferon therapy.

Quality of the evidence

GRADE assessments

GRADEPro was used to create 'Summary of findings' tables for the various outcomes. In determining the level of evidence for each outcome, both the efficacy results and the assessment of the risk of bias were integrated into a final assessment of the level of evidence and full details of the decision provided in footnotes. All primary and secondary outcomes were rated as critical and received a score of '9' indicating the highest level of importance to patients.

Interferon and chemotherapy versus chemotherapy alone

See Summary of findings for the main comparison for the complete assessment and rationale for ratings.

For the outcome of overall survival the level of evidence was rated as low. The evidence is based on the findings of two trials. The reasons for downgrading this outcome is due to the method of randomisation not being described in the included trials and allocation concealment either not being described or undertaken, as well as one trial being stopped early.

For disease progression and adverse events (flu-like symptoms, fatigue and neurotoxicity) the level of evidence was rated as low. Reasons for this rating included lack of reporting on the method of randomisation, allocation concealment either not described or undertaken in the trials, significant heterogeneity between the trials, high risk of bias due to stopping the trial early, and small sample sizes and potential for a study to be underpowered to detect the true effect of the intervention on the outcome in question.

Interferon versus observation alone

See Summary of findings 2 for the complete assessment and rationale for ratings.

For the outcome of overall survival the level of evidence was rated as low. The evidence was based on the findings of two small trials with unclear or potentially high risk of selection bias and performance bias. In addition to this, the wide confidence intervals reflect imprecise estimates of effect for this outcome.

For disease progression and adverse events (nausea and vomiting, flu-like symptoms and fatigue) the level of evidence was rated as low. Evidence for these outcomes was based on the findings of one study that did not report the method of randomisation or describe how allocation concealment was conducted, or if it was conducted, resulting in unclear or potentially high risk of selection bias. The small sample size and potential for a study to be underpowered to detect the true effect of the intervention on the outcome in question also led to the quality of the evidence being downgraded.

Based on the low quality of evidence for the outcomes reported, there is insufficient evidence for a robust conclusion regarding the effectiveness of interferon in the treatment of advanced EOC. This is based on the results of the four trials that were included in the meta-analyses. The key methodological shortcomings were the absence of the method of randomisation and allocation concealment, significant heterogeneity between trials, small sample sizes as well as early stoppage of trials.

Potential biases in the review process

Biases in the review process were minimised by performing a comprehensive search of the literature, independently selecting and appraising the trials, and extracting the data in duplicate. Where data were missing, we sought additional information and data direct from authors, where this was possible to do so. At the time of the review submission, we were unable to get information on various methodological aspects of the trials (for example method of randomisation and allocation concealment) as well as important outcomes (for example number of deaths, number of participants with disease progression or recurrence) from the relevant authors.

The following aspects of the included trials could introduce bias into the results of the review.

- Although all of the included trials investigated interferon, the interventions evaluated in the trials were similar but not identical.
- Interferon was administered either subcutaneously or intraperitoneally.
- The chemotherapy regimes used, either in combination with interferon or prior to interferon therapy, were similar but not identical.

The review is at risk of publication bias for less prominent trials. We attempted to reduce this risk by identifying relevant conference abstracts, by handsearching relevant conference proceedings. Furthermore, there are two trials awaiting assessment as we could not get hold of the full text articles. It is not known what effect the results of these trials might have on the validity of this review.

Agreements and disagreements with other studies or reviews

Windbichler 2000 concluded that the inclusion of intraperitoneal INFγ in first-line chemotherapy prolongs progression free survival. This finding is similar to that of a pilot study by Berek 2000, which found surgically documented responses in the size of ovarian tumours following the use of INFα. Overall this review concluded that interferon, with or without chemotherapy, was no more effective than chemotherapy alone or observation alone in improving overall survival or progression free survival in post-surgical women with advanced epithelial ovarian cancer (EOC).

In a study by Freedman 1983, where human leukocyte INFα was administered to 15 patients with EOC after previous chemotherapy or therapeutic irradiation, one objective response was observed. In another study by Epstein 1980, which determined the in vitro sensitivity of human ovarian carcinoma cells to the antiproliferative effects of human leukocyte interferon, tumour colony cells were found to be responsive to interferon. In a preliminary trial by Jui-Tung 1992, where INFα and INFγ with sizofiran were given to post-operative patients, it was found that there were no recurrences in those patients. There was also significant difference in survival in the patients treated with interferon.

AUTHORS' CONCLUSIONS

Implications for practice

Based on low quality evidence, the addition of interferon to first-line chemotherapy, compared with chemotherapy alone, did not alter the overall survival in post-surgical women with advanced EOC. There is low quality evidence to support that interferon in combination with chemotherapy, compared with chemotherapy alone, worsened the progression free survival in post-surgical women with advanced EOC. There is not enough evidence that interferon therapy alone alters overall survival or progression free survival compared to observation alone in post-surgical women who have undergone first-line chemotherapy.

Implications for research

Three of the five trials included in this review were stopped early and may be underpowered to detect the true effect of the intervention. The trials did not report the results of important outcomes in a uniform manner, preventing statistical aggregation of the results. Trial methodology was poorly reported, resulting in unclear risk of bias. For clear recommendations to be made regarding the effectiveness of interferon in the treatment of advanced EOC, long-term, well conducted and adequately powered RCTs would be needed to investigate the effects of interferon on overall survival, progression free survival, complete clinical response, quality of life, adverse events and cost implications. Improved trial planning and conduct are necessary to avoid early stoppage of trials. However, the available data do not suggest that interferon has a clinically significant effect in EOC, either alone or combined with conventional chemotherapy, hence conducting further studies might not be ethical.

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, NHS or the Department of Health

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Alberts 2006

Methods	Randomised controlled trial Trial duration: 11 years, from March 1988 to June 1999 Trial location: USA - 66 participants from South West Oncology Group (SWOG) and 4 from Gynecologic Oncology Group (GOG)
Participants	Number of participants: 70 randomised (35 treatment group, 35 observation alone) Inclusion criteria: • Histologically proven advanced (stage II or III) ovarian cancer • 120 days or less elapsed between completion of chemotherapy and second-look surgery • South West Oncology Group performance status of 0-2 • White blood cell (WBC) ≥3500µl, platelet count ≥100,000/µl, adequate renal and hepatic function • Patent intraperitoneal space at the time of second-look surgery • Registered no later than 42 days following second-look surgery Exclusion criteria: not specified
Interventions	Intervention: Alpha-interferon (IFNα-26, Schering-Plough Kenilworth, NJ) in weekly doses of $50x10^6$ IU (for 6 doses) Control: observation alone
Outcomes	• Overall survival • Progression free survival, definition was not specified • Adverse events: abdominal pain/cramping, alopecia, anemia, arthralgia, catheter-related infection, diarrhea without colostomy, dizziness/lightheadedness, dyspenia, fatigue/malaise/lethargy, fever without neutropenia, fever, flu-like symptoms, headache, hypotension, leukopenia, local injection site reaction, myalgia/ arthralgia, nausea, neutropenia/granulocytopenia, pain, rigors/chills, SGOT (AST) increase, sensory neuropathy, urinary tract infection, vomiting
Notes	Ethics approval: the trial received local institutional review board (IRB) review and approval according to institutional guidelines Informed consent: IRB approved consent forms were signed by the patients Funding: source of funding/conflict of interest not declared Correspondence with authors: dalberts@azcc.arizona.edu on the 3rd July 2012

Risk of bias

Alberts 2006 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It is reported that patients were randomised but the method of randomisation is not described
Allocation concealment (selection bias)	Unclear risk	Not reported on
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported on. Control group was merely observed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up was minimal and similar in both groups (3/35 intervention, 0/35 control)
Selective reporting (reporting bias)	Unclear risk	Protocol was not obtained
Other bias	Unclear risk	Trial stopped early due to poor accrual of patients

Alberts 2008

Methods	This was a multicentre, open-label, two-arm phase III randomised controlled trial Trial duration: enrolment from January 29, 2002 to March 31, 2004. Trial duration not specified Trial location: Europe, North and South America
Participants	Number of participants: 847 participants (426 intervention, 421 control), 774 ovarian cancer (OC), 73 primary peritoneal carcinoma (PPC) Inclusion criteria: • Previously untreated females with histologically confirmed epithelial ovarian cancer or PPC and FIGO Stage III or IV with either optimal or suboptimal residual disease following initial surgery • The majority of patients were Stage III O.C patients with 76.5% and 76.7% in the experimental group and comparison groups respectively. Stage IV 23.5% and 23.3% respectively • Randomisation within 12 weeks after initial surgery • Seven days or less between randomisation and first treatment dose • Adequate bone marrow, hepatic and renal function • Eastern Cooperative Oncology Group performance score of 0-2 Exclusion criteria: not stated
Interventions	Intervention: Chemotherapy plus interferon-gamma 1b (IFN-γ 1b) Chemotherapy included paclitaxel (175 mg/m^2 over 3 hours) followed by carboplatin (AUC 6) every 3 weeks. A total of 6 cycles of chemotherapy were given unless disease progression or dose-limiting toxicity occurred or patients refused further treatment

Alberts 2008 *(Continued)*

	Interferon therapy included 100µg administered subcutaneously, 3 times weekly (every other day; no more than 3 days in a 7-day period) continuously (including the 3 weeks following the last dose of chemotherapy) Control: Chemotherapy alone consisting of Paclitaxel (175 mg/m^2 over 3 hours) followed by carboplatin (AUC 6) every 3 weeks. A total of 6 cycles of chemotherapy were given unless disease progression or dose-limiting toxicity occurred or patients refused further treatment
Outcomes	• Overall survival (OS): time (days) from the time of randomisation until death • Progression free survival (PFS): time (days) from randomisation until the earliest date of disease progression, death, or censoring • Treatment-failure free survival (TFFS): time (days) from randomisation until the earliest date of progressive disease, death, or the start of non-protocol carcinoma treatment for any reason • Adverse events (any, skin, blood, gastrointestinal, general, nervous system, musculoskeletal, infectious, psychiatric, metabolism, immune, investigations)
Notes	Ethics approval: this was not reported on Informed consent: patients provided informed consent between January 29, 2002 and March 31, 2004 Funding: this was not reported on Correspondence with authors: dalberts@azcc.arizona.edu on 3rd July 2012

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned how randomisation was carried out
Allocation concealment (selection bias)	Unclear risk	Not reported on
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label trial but unlikely to affect outcomes. Control group received chemotherapy alone
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Disease progression was assessed by an endpoint review committee blinded to the treatment assignment using serial CT scans, MRIs, physical exams, and CA-125 levels
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis was done 79% of participants adhered to treatment (i.e, undertook at least 5 out of 6 courses) in the treatment arm and 86% adhered in the control arm. 34% of adherent participants died in the intervention arm while 28% died in the control arm. 61% of non-adherent participants died in the intervention arm while 45% of non-adherent participants died in the control arm.
Selective reporting (reporting bias)	Unclear risk	Protocol was not available
Other bias	Unclear risk	Study stopped early due to DSMB (data and safety monitoring board) recommendation - this was due to the study finding a statistically significant differ-

Alberts 2008 *(Continued)*

	ence between treatment groups that crossed the pre-specified boundaries for inferiority and futility.

Bruzzone 1997

Methods	Randomised controlled trial Trial duration: 4 years June 1990 to October 1992 Trial location: Italy (North West Oncology group)
Participants	Number of participants: 111 randomised (57 experimental group, 54 control) Inclusion criteria: • Patients with advanced epithelial ovarian cancer • Age between 18 and 75 years • ECOG performance status 0,1 or 2 • Participant with FIGO Stage I/II, III, IV ovarian cancer in the intervention group to be 4%, 83% and 13% and the the control group patient in FIGO Stage III and IV were 86% and 14% respectively • Good renal, haematological, hepatic and cardiac function • More than 3 months life expectancy • Patients informed consent Exclusion criteria: • Previous or concomitant malignancy • Extra-abdominal localisations of disease
Interventions	Intervention: Intraperitoneal INF-alpha 25,000,000 U on day 1 followed by intraperitoneal carboplatin 400mg/m^2 on day 2 every 28 days for 3 courses Control: Intraperitoneal carboplatin 400mg/m^2 every 28 days
Outcomes	• Overall survival • Progression free survival - assessment of PFS was first progression and death without a confirmed progression • Toxicity - leukopenia, anaemia, renal, neurologic and gastroenteric toxicity, flu-like syndrome
Notes	Ethics approval: not reported on Informed consent: participants signed informed consent forms before enrolment into study Funding: source of funding not reported on. Probably under auspices of North West Oncology Group Correspondence with authors: National Institute for Cancer Research and Co-operative Centers of the North West Oncology Group on 3rd July 2012

Risk of bias

Bias	Authors' judgement	Support for judgement

Bruzzone 1997 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomisation was performed using random number tables and specific lists of randomisation numbers
Allocation concealment (selection bias)	Low risk	Treatment allocation was conducted centrally by telephoning the trial office at the Cancer Institute whenever a patient was enrolled
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants was not reported on but measured outcomes unlikely to be affected by lack of blinding as control group received chemotherapy only
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up low and similar in both groups (5/57 intervention, 5/54 control). Intention-to-treat analysis was also conducted
Selective reporting (reporting bias)	Unclear risk	Trial protocol not obtained
Other bias	Unclear risk	Trial stopped early due to due to toxicities and the higher costs in the interferon arm considering the absence of impressive survival advantage

Hall 2004

Methods	Randomised controlled trial Trial duration: 7 years and 5 months, from February 1990 to July 1997 Trial location: 14 centres across the United Kingdom
Participants	Number of participants: 300 randomised (interferon-149, control-151) Inclusion criteria: Patients had histologically proven epithelial ovarian cancer that showed no evidence of disease progression after post-operative chemotherapy. The percentage of participants with FIGO stage I, II, III and IV ovarian cancer in the interferon group was 7%, 22%, 63% and 15% while in the chemotherapy group was 8%, 13%, 64% and 15% respectively Exclusion criteria: not specified
Interventions	Intervention: Interferon-alpha: INF-α 2a (Roferon-A, Roche) (4.5 mega-units subcutaneously 3 days per week). Interferon was continued until disease progression or in response to toxicity or patient request Control: No maintenance treatment
Outcomes	• Overall survival (OS) • Progression free survival (PFS), definition was not given

Hall 2004 *(Continued)*

	• Toxicity/adverse event (flu-like symptoms, fatigue, nausea/vomiting, neurological, dyspnoea, depression/anxiety, skin change/rash, alopecia, arthralgia/arthritis, insomnia, haematological, hepatic, injection site reaction, other, not stated)
Notes	Ethics approval: study was approved by the Local Research Ethics Commitee of each participating centre Informed consent: written informed consent was obtained from patients prior to randomisation Funding: not mentioned Correspondence with authors: g.hall@leeds.ac.uk on date on 3rd July 2012

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described how randomisation was done
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described if participants were blinded to the treatment assigned. Control group did not receive any treatment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described if outcome assessors were blinded to treatment assignment but inlikely to have any effect on the outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat (ITT) analysis was done on all the patients. Eight patients (2 interferon and 6 observation) died without any follow-up visits). 144 of 149 participants in the interferon group received at least one injection
Selective reporting (reporting bias)	Unclear risk	Protocol was not available
Other bias	Low risk	No reason to suspect other bias

Windbichler 2000

Methods	Randomised controlled trial Trial duration: 7 years and 3 months, from December 1991 to March 1998 Trial location: 12 Austrian gynaecological and medical centres
Participants	Number of participants: 148 randomized (75 intervention group, 73 control group) Inclusion criteria: • Patients who had undergone primary surgical debulking of histologically confirmed invasive epithelial ovarian cancer in FIGO Stages Ic-III, with WHO performance status 0-2 • The percentage of women with FIGO Stage Ic, II, III and IV ovarian cancer in the interferon group were 11%, 14%, 74% and 1% respectively while in the chemotherapy group were 16%, 9%, 69% and 6% respectively

Windbichler 2000 *(Continued)*

	• Adequate renal function • Sufficient hepatic function • WBC > 3g/l, platelet count ≥ 100g/l • Age less than 75 years Exclusion criteria: Patients with concomitant severe cardiovascular disease, life expectancy of less than 3 months, recent second malignancy or history of thromboembolic disease
Interventions	Intervention: Intraperitoneal treatment with interferon-gamma (IFN-γ) consisting of 0.1 mg subcutaneously on days 1,3,5, 15, 17 and 19 of each 28-day cycle PLUS standard chemotherapy given every 4 weeks consisting of 100mg/m^2 cisplatin and 600mg/m^2 cyclophosphamide Control: Standard chemotherapy given every 4 weeks consisting of 100mg/m^2 cisplatin and 600mg/m^2 cyclophosphamide
Outcomes	• Overall survival (OS) • Progression free survival (PFS), PFS was defined as the interval between the initial surgery and last follow-up evaluation, diagnosis of progression or death from disease, whichever occurred first • Response • Toxicity (anaemia, neutropenia, thrombocytopenia, creatinine, bilirubin, SGOT, emesis, alopecia)
Notes	Ethics approval: study protocol was approved by the Ethical Committee of the University of Innsbruck Medical School as well as the respective committees of the other participating centres Informed consent: all participants signed written consent forms before being enrolled Funding: not mentioned Correspondence with authors: To C Marth. Department of Obstetrics and Gynaecology, University Hospital, Anichstrasse 35, A-6020 Innsbruck, Austria 3rd July 2012

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation lists were computer generated
Allocation concealment (selection bias)	Low risk	Patients were allocated to a treatment arm by the study centre by means of fax transmission
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not mentioned but unlikely to affect the study outcomes. Control group received chemotherapy only
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned. Unlikely to affect the study as outcomes are objective. All slides were reviewed by one pathologist
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis was done. In the treatment group 6 of 65 patients discontinued due to disease progression. Of the remaining 59 participants, 32 completed 6 cycles of treatment. In the control group, 7 of the 68 partici-

Windbichler 2000 *(Continued)*

		pants discontinued due to disease progression. Of the remaining 61 patients, 39 completed 6 cycles of chemotherapy
Selective reporting (reporting bias)	Unclear risk	Protocol was not available
Other bias	Low risk	No reason to suspect other bias

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

Study	Reason for exclusion
Berek 2000	Not a randomised controlled trial
Cardamakis 1999	Not a randomised controlled trial
Sumrit 1998	Abstract or full article not found

Characteristics of studies awaiting assessment *[ordered by study ID]*

Kosmidis 1997

Methods	Not specified
Participants	83 women with median age 56 years. 74% had stage III while 435 had serious and 25% had mucinous adenocarcinoma. 30% had an optimal operation with residual disease and treated with chemotherapy. Of the 86 women 44 had complete clinical remission (cCR) and they were randomised to receive either interferon-alpha 2b or observation alone
Interventions	Intervention: Intraperitoneal interferon was given Control: Patients were observed
Outcomes	• Overall survival • Feasibility of interferon • Tolerance of interferon
Notes	The full text article has been requested from authors but we have not received any response.

Zhyl'chuk 1998

Methods	Not specified
Participants	Participants with different histologic forms of ovarian cancer
Interventions	Adjuvant interferon

Zhyl'chuk 1998 *(Continued)*

Outcomes	CA-125 levels
Notes	The full text article has been requested from authors but we have not received any response.

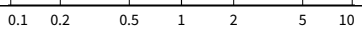
DATA AND ANALYSES

Comparison 1. Interferon versus observation alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	2	370	Hazard Ratio (Random, 95% CI)	1.14 [0.84, 1.55]
2 Progression-Free Survival	2	370	Hazard Ratio (Random, 95% CI)	0.99 [0.79, 1.24]
3 Adverse event (flu-like symptoms)	1	293	Risk Ratio (M-H, Random, 95% CI)	2.25 [1.73, 2.91]
4 Adverse event (fatigue)	1	293	Risk Ratio (M-H, Random, 95% CI)	1.54 [1.27, 1.88]
5 Adverse event (nausea/ vomiting)	1	293	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.91, 1.62]

Analysis 1.1. Comparison 1 Interferon versus observation alone, Outcome 1 Overall survival.

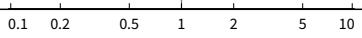
Study or subgroup	Interferon N	Observation alone N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
Alberts 2006	35	35	0.5 (0.342)		18.98%	1.58[0.81,3.09]
Hall 2004	149	151	0.1 (0.133)		81.02%	1.06[0.82,1.38]
Total (95% CI)					**100%**	**1.14[0.84,1.55]**
Heterogeneity: Tau²=0.01; Chi²=1.19, df=1(P=0.28); I²=15.84%						
Test for overall effect: Z=0.85(P=0.39)						



Favours interferon — Favours observation alone

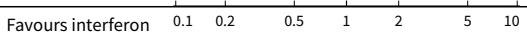
Analysis 1.2. Comparison 1 Interferon versus observation alone, Outcome 2 Progression-Free Survival.

Study or subgroup	Interferon N	Observation alone N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
Alberts 2006	35	35	0.2 (0.309)		13.87%	1.2[0.65,2.19]
Hall 2004	149	151	-0 (0.124)		86.13%	0.96[0.75,1.22]
Total (95% CI)					**100%**	**0.99[0.79,1.24]**



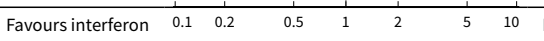
Favours interferon — Favours observation alone

Study or subgroup	Interferon	Observation alone	log[Hazard Ratio]	Hazard Ratio	Weight	Hazard Ratio
	N	N	(SE)	IV, Random, 95% CI		IV, Random, 95% CI
Heterogeneity: Tau²=0; Chi²=0.44, df=1(P=0.51); I²=0%						
Test for overall effect: Z=0.09(P=0.93)						



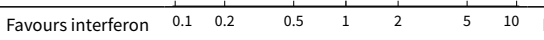
Analysis 1.3. Comparison 1 Interferon versus observation alone, Outcome 3 Adverse event (flu-like symptoms).

Study or subgroup	Interferon	Observation alone	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Hall 2004	102/144	47/149		100%	2.25[1.73,2.91]
Total (95% CI)	**144**	**149**		**100%**	**2.25[1.73,2.91]**
Total events: 102 (Interferon), 47 (Observation alone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=6.13(P<0.0001)					



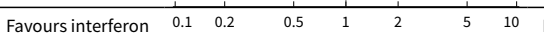
Analysis 1.4. Comparison 1 Interferon versus observation alone, Outcome 4 Adverse event (fatigue).

Study or subgroup	Interferon	Observation alone	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Hall 2004	106/144	71/149		100%	1.54[1.27,1.88]
Total (95% CI)	**144**	**149**		**100%**	**1.54[1.27,1.88]**
Total events: 106 (Interferon), 71 (Observation alone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.38(P<0.0001)					



Analysis 1.5. Comparison 1 Interferon versus observation alone, Outcome 5 Adverse event (nausea/ vomiting).

Study or subgroup	Interferon	Observation alone	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Hall 2004	61/144	52/149		100%	1.21[0.91,1.62]
Total (95% CI)	**144**	**149**		**100%**	**1.21[0.91,1.62]**
Total events: 61 (Interferon), 52 (Observation alone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.31(P=0.19)					

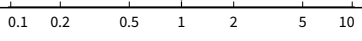


Comparison 2. Interferon + chemotherapy versus chemotherapy alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	2	244	Hazard Ratio (Random, 95% CI)	1.14 [0.74, 1.76]
2 Progression-Free Survival	2	244	Hazard Ratio (Random, 95% CI)	1.43 [1.02, 2.00]
3 Complete clinical response	1	81	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.87, 1.73]
4 Adverse event (flu-like symptoms)	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Adverse event (fatigue)	1	97	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.82, 1.68]
6 Adverse event (neurotoxicity)	2	230	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.57, 1.33]
7 Adverse event (alopecia)	2	230	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.74, 1.23]
8 Adverse event (anaemia)	2	230	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.83, 1.55]

Analysis 2.1. Comparison 2 Interferon + chemotherapy versus chemotherapy alone, Outcome 1 Overall survival.

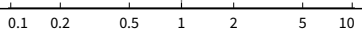
Study or subgroup	Interferon + chemo N	Chemo alone N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
Bruzzone 1997	57	54	0 (0.302)		53.05%	1.04[0.57,1.88]
Windbichler 2000	65	68	0.2 (0.321)		46.95%	1.27[0.68,2.38]
Total (95% CI)					**100%**	**1.14[0.74,1.76]**
Heterogeneity: Tau²=0; Chi²=0.2, df=1(P=0.65); I²=0%						
Test for overall effect: Z=0.6(P=0.55)						



Favours interferon +chemo — Favours chemo alone

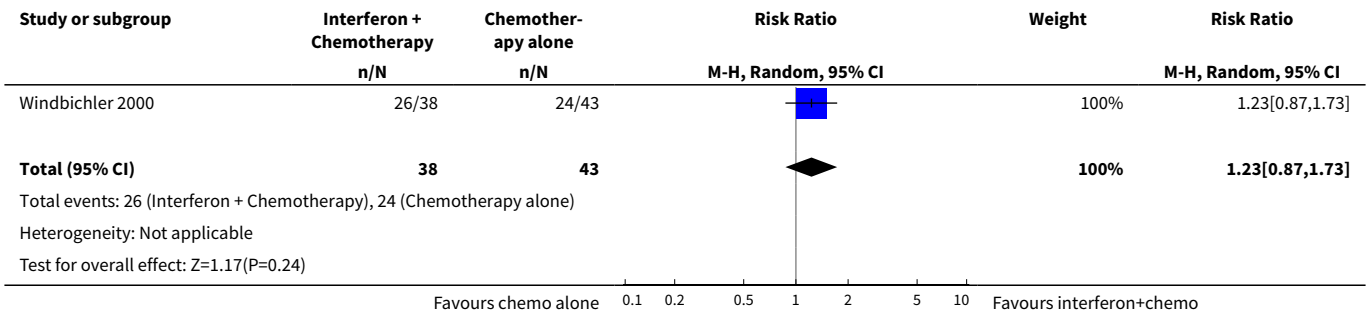
Analysis 2.2. Comparison 2 Interferon + chemotherapy versus chemotherapy alone, Outcome 2 Progression-Free Survival.

Study or subgroup	Interferon + Chemotherapy N	Chemotherapy alone N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
Bruzzone 1997	57	54	0.3 (0.239)		51.44%	1.3[0.82,2.08]
Windbichler 2000	65	68	0.5 (0.246)		48.56%	1.58[0.98,2.56]
Total (95% CI)					**100%**	**1.43[1.02,2]**
Heterogeneity: Tau²=0; Chi²=0.32, df=1(P=0.57); I²=0%						
Test for overall effect: Z=2.09(P=0.04)						

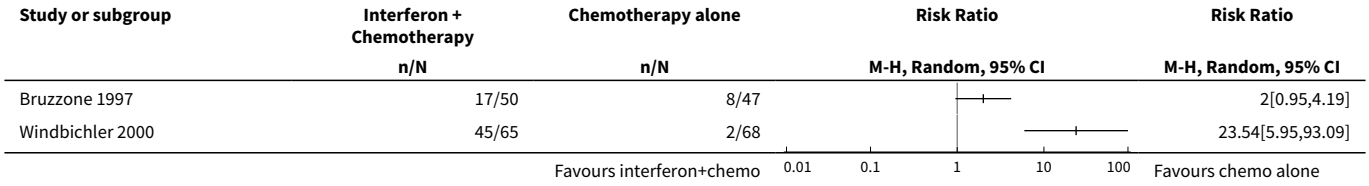


Favours interferon +chemo — Favours chemo alone

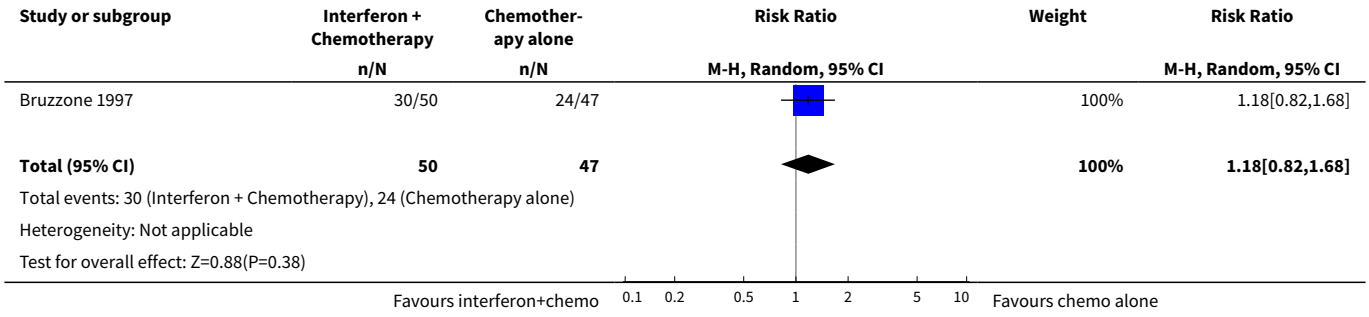
Analysis 2.3. Comparison 2 Interferon + chemotherapy versus chemotherapy alone, Outcome 3 Complete clinical response.



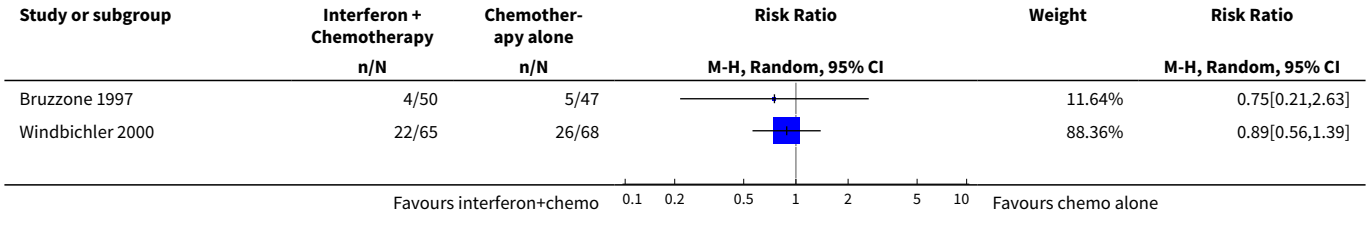
Analysis 2.4. Comparison 2 Interferon + chemotherapy versus chemotherapy alone, Outcome 4 Adverse event (flu-like symptoms).

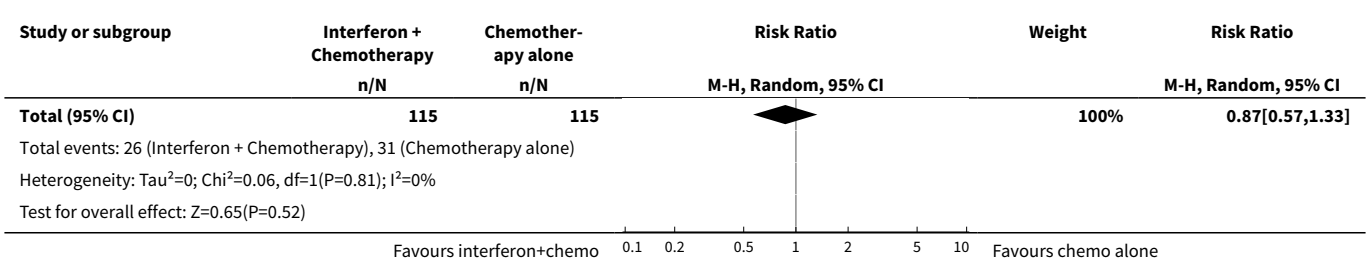


Analysis 2.5. Comparison 2 Interferon + chemotherapy versus chemotherapy alone, Outcome 5 Adverse event (fatigue).

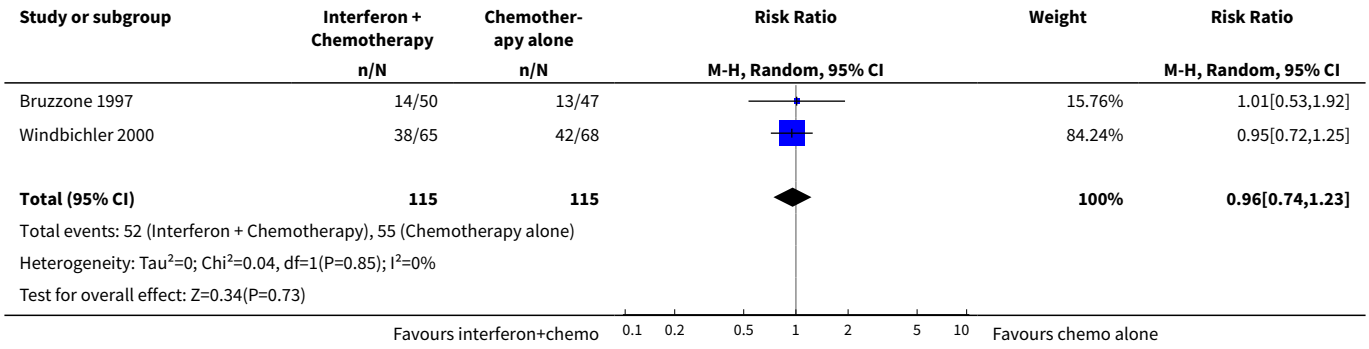


Analysis 2.6. Comparison 2 Interferon + chemotherapy versus chemotherapy alone, Outcome 6 Adverse event (neurotoxicity).

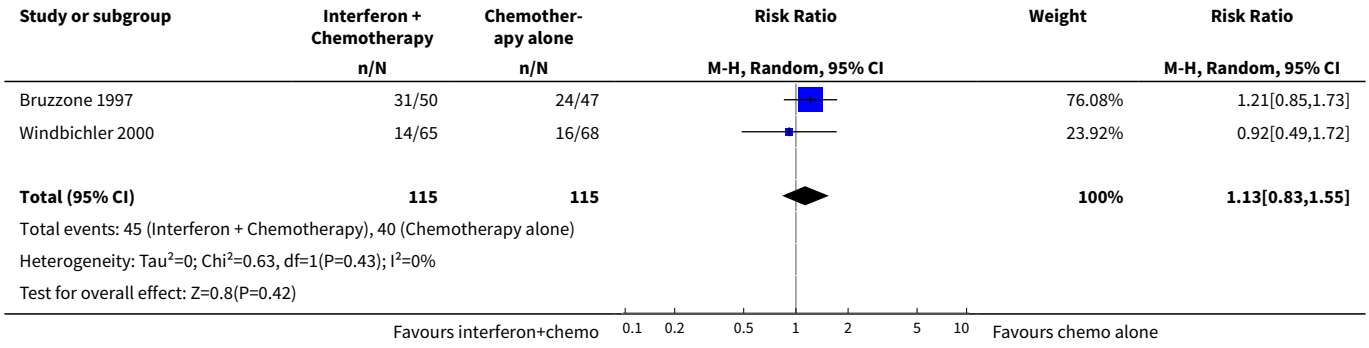




Analysis 2.7. Comparison 2 Interferon + chemotherapy versus chemotherapy alone, Outcome 7 Adverse event (alopecia).



Analysis 2.8. Comparison 2 Interferon + chemotherapy versus chemotherapy alone, Outcome 8 Adverse event (anaemia).



ADDITIONAL TABLES

Table 1. Table 1: FIGO staging for ovarian cancer

STAGE I	The cancer is limited to the ovaries

Table 1. Table 1: FIGO staging for ovarian cancer *(Continued)*

IA	Limited to one ovary and the outer ovarian capsule is not ruptured. There is no tumor on the external surface of the ovary and there is no ascites and/or the washings are negative
IB	Cancer is present in both ovaries, but the outer capsule is intact and there is no tumor on external surface. There is no ascites and the washings are negative
IC	The cancer is either Stage IA or IB level but the capsule is ruptured or there is tumor on the ovarian surface or malignant cells are present in ascites or washings
STAGE II	Cancer involves one or both ovaries with spread to other pelvic organs or surfaces
IIA	Extension or implants onto the uterus and/or fallopian tube. The washings are negative washings and there is no ascites
IIB	Extension or implants onto other pelvic tissues. The washings are negative and there is no ascites
IIC	Pelvic extension or implants like Stage IIA or IIB but with positive pelvic washings
STAGE III	Cancer spread outside the pelvis to the abdominal area, including metastases to liver surface
IIIA	Tumor is grossly confined to the pelvis but with micro-scopic peritoneal metastases beyond pelvis to abdominal peritoneal surfaces or the omentum
IIIB	Same as IIIA but with macro-scopic peritoneal or omental metastases beyond pelvis less than 2 cm in size
IIIC	Same as IIIA but with peritoneal or omental metastases beyond pelvis, larger than 2 cm or lymph node metastases to inguinal, pelvic, or para-aortic areas
STAGE IV	Metastases or spread to the liver or outside the peritoneal cavity to areas such as the chest or brain

APPENDICES

Appendix 1. MEDLINE search strategy

Medline Ovid

1 exp Ovarian Neoplasms/
2 (ovar* adj5 (cancer* or tumor* or tumour* or neoplas* or malignan* or carcinoma* or adenocarcinoma*)).mp.
3 1 or 2
4 exp Interferons/
5 interferon*.mp.
6 (Infergen or Roferon-A or Alferon-N or Avonex or Betaseron or Actimmune).mp.
7 4 or 5 or 6
8 randomized controlled trial.pt.
9 controlled clinical trial.pt.
10 randomized.ab.
11 placebo.ab.
12 drug therapy.fs.
13 randomly.ab.
14 trial.ab.
15 groups.ab.
16 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17 3 and 7 and 16

key:

mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier, pt=publication type, ab=abstract, fs=floating subheading

Appendix 2. EMBASE search strategy

Embase Ovid

1 exp ovary cancer/
2 (ovar* adj5 (cancer* or tumor* or tumour* or neoplas* or malignan* or carcinoma* or adenocarcinoma*)).mp.
3 1 and 2
4 exp interferon/
5 interferon*.mp.
6 (Infergen or Roferon-A or Alferon-N or Avonex or Betaseron or Actimmune).mp.
7 4 or 5 or 6
8 crossover procedure/
9 double-blind procedure/
10 randomized controlled trial/
11 single-blind procedure/
12 random*.mp.
13 factorial*.mp.
14 (crossover* or cross over* or cross-over*).mp.
15 placebo*.mp.
16 (double* adj blind*).mp.
17 (singl* adj blind*).mp.
18 assign*.mp.
19 allocat*.mp.
20 volunteer*.mp.
21 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22 3 and 7 and 21

key:

mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword

Appendix 3. CENTRAL search strategy

CENTRAL

#1 MeSH descriptor Ovarian Neoplasms explode all trees
#2 (ovar* near/5 (cancer* or tumor* or tumour* or neoplas* or malignan* or carcinoma* or adenocarcinoma*))
#3 (#1 OR #2)
#4 MeSH descriptor Interferons explode all trees
#5 interferon*
#6 (Infergen or Roferon-A or Alferon-N or Avonex or Betaseron or Actimmune)
#7 (#4 OR #5 OR #6)
#8 (#3 AND #7)

WHAT'S NEW

Date	Event	Description
17 July 2018	Amended	Next stage expected date amended.
28 June 2018	Review declared as stable	Intervention no longer in general use.

HISTORY

Protocol first published: Issue 2, 2012
Review first published: Issue 6, 2013

Date	Event	Description
1 April 2015	Amended	Contact details updated.
24 February 2015	Amended	Contact details updated.
11 February 2015	Amended	Contact details updated.
27 March 2014	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

AL developed the protocol with the assistance of AM. AM wrote the data collection and analysis section and also assisted in the writing of the background. LN wrote various sections of the review and edited all of the versions of the review.

DECLARATIONS OF INTEREST

Aramide Lawal: none known

Alfred Musekiwa: none known

Liesl Grobler: none known

SOURCES OF SUPPORT

Internal sources

- Wits Reproductive Health & HIV Institute (WRHI), University of Wits, Johannesburg, South Africa.
- Faculty of Health Sciences, Stellenbosch University, Cape Town, South Africa.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have used the Parmar's methods to calculate hazard ratios and their corresponding standard errors. This was not specified in the protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents [adverse effects] [*therapeutic use]; Carcinoma, Ovarian Epithelial; Disease-Free Survival; Interferons [adverse effects] [*therapeutic use]; Neoplasms, Glandular and Epithelial [*drug therapy] [mortality] [pathology] [surgery]; Ovarian Neoplasms [*drug therapy] [mortality] [pathology] [surgery]

MeSH check words

Female; Humans