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Review article

Gemcitabine for recurrent ovarian cancer - a systematic review and meta-analysis

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HIGHLIGHTS

- First systematic review and metaanalysis on gemcitabine for recurrent ovarian cancer.
- Six RCTs evaluating the efficacy and safety of gemcitabine in recurrent ovarian cancer.
- The evidence for single-agent gemcitabine might not reflect the way it is used today.

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ABSTRACT

Introduction: More than 80 % of women with advanced ovarian cancer relapse either during or after adjuvant therapy. Platinum-sensitive women are rechallenged with a platinum-combination therapy and platinum-resistant women are challenged with non-platinum drugs.
Gemcitabine is one of many treatments that can be used both as single-agent or as combination therapy for the treatment of recurrent ovarian cancer.
Methods: We included all randomised controlled trials investigating patients treated with gemcitabine for recurrent ovarian cancer and reporting data on overall survival, progression-free survival and toxicity. CENTRAL, EMBASE and MEDLINE were searched on the 31st of May 2019.
Results: We included six randomised controlled trials that evaluated gemcitabine either alone or as combination therapy.
Two studies compared gemcitabine to pegylated liposomal doxorubicin in women with platinum-resistant recurrent ovarian cancer. Difference in overall and progression-free survival was non-significant. Gemcitabine treatment was associated with significantly more neutropenia, whereas pegylated liposomal doxorubicin was associated with significantly more hand-foot syndrome.
One study evaluated carboplatin and gemcitabine to carboplatin. Difference in overall survival was non-significant, but progression-free survival was longer with gemcitabine and carboplatin (HR: 0.72, 95% CI 0.58–0.9).
One study evaluated gemcitabine with gemcitabine and pertuzumab. Overall survival and progression-free survival was similar between the two arms.
One study compared gemcitabine and carboplatin to gemcitabine, carboplatin and bevacizumab. Overall survival was similar in the two arms. Progression-free survival was significantly better in the bevacizumab arm (HR 0.48 95% CI 0.39–0.61).
One study compared etoposide and gemcitabine to etoposide. The study showed similar overall survival and progression-free survival.
Discussion: The results show that gemcitabine is an active and safe agent in the treatment of both platinum-sensitive and resistant recurrent ovarian cancer but might highlight the need of new randomised studies in heavily pre-treated patients.

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Contents

1. Introduction

Cancers originating from either the ovaries, fallopian tubes or primary peritoneal cancer are denoted as ovarian cancer (OC). Ovarian cancer is the 10th most frequent cancer among women and has the highest mortality among gynaecological cancers. In the United States an estimated 22.530 new cases will be diagnosed in 2019 and 13.980 deaths [1]. More than 75% are diagnosed with advanced (stage III or IV) disease due to unspecific symptoms and lack of screening [2]. The five-year survival is 25–30% for advanced ovarian cancer [2,3].

Treatment of recurrent ovarian cancer (ROC) is dependent of platinum-sensitivity. Former guidelines described platinum-sensitive ROC as women with at platinum-free interval (PFI) of more than six months and platinum-resistant as a PFI of less than six months. The new definition by ESMO-ESGO guidelines divide resistant and sensitive disease in either proven or assumed resistance or sensitivity. Proven platinum sensitivity is defined as a previous response to platinum where assumed sensitivity is previous response without an early symptomatic relapse. Proven platinum resistance is seen as progression during platinum therapy and assumed resistance is based upon early symptomatic relapse [4].

Women with platinum-sensitive ROC are offered treatment with carboplatin and liposomal doxorubicin (PLD) unless evidence of contraindications. This is due to two trials (MITO-2 and Pujade-Lauraine et al.) showing similar efficacy compared to carboplatin and paclitaxel, but less toxicity [5,6].

Women with platinum-resistant ROC are often treated with single agents as PLD, paclitaxel or gemcitabine. The NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) and ESMO-ESGO guidelines do not recommend a certain sequence of systemic therapy regimens for patients requiring multiple courses of therapy for recurrent disease, but recommends that the choice of therapy should be based on toxicity and patient preferences. [4,7].

Gemcitabine is a pyrimidine antagonist that inhibits DNA synthesis by targeting cells in the S-phase. Gemcitabine is metabolised intracellularly to active diphosphate and triphosphate nucleosides. The metabolites inhibits DNA synthesis by ribonucleotide reductase which reduces the concentration of deoxynucleosides as well as competes with dCTP for incorporation into DNA [8].

Gemcitabine was tested in a randomised phase III trial in combination with carboplatin versus carboplatin published in 2006 that showed a hazard ratio for progression-free survival of 0.72 (95% CI 0.58–0.9) and response rates of 47.2% (CI 95% 39.9%–54.5%) versus 30.9% (95% CI 24.1%–37.7%) [9].

The recommended dose in combination with carboplatin is 1000mg/m2 administered day 1 and 8 in a 21-day cycle. Gemcitabine is given as 1000mg/m2 administered day 1, 8 and 15 when given as single agent therapy.

Gemcitabine with carboplatin for platinum-sensitive ovarian cancer has been proved to be equivalent to carboplatin, but due to MITO-2 and Pujade-Lauraine the preferred treatment is carboplatin and PLD [5,6,9].

The treatment of ROC requires a careful consideration regarding quality of life, and it is therefore important to base treatment on not only efficacy but also tolerability. To our knowledge a systematic review of gemcitabine for recurrent ovarian cancer has not been done. By conducting a thorough systematic review of randomised controlled trials (RTCs) of gemcitabine in women with both platinum-sensitive and platinum-resistant ROC we aimed to examine gemcitabine's efficacy and safety compared to other chemotherapeutic options.

2. Materials and methods

This systematic review and meta-analysis were reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) an evidence-based guideline for conducting systematic reviews and meta-analyses [10]. The protocol was registered to the International Prospective Register of Systematic Review (PROSPERO) with registration number CRD42018093055 [11].

The following criteria were evaluated in selecting articles for inclusion (PICOS):

Population: Women with recurrent ovarian cancer of any stage and any platinum-free interval.

Intervention and comparison: All studies where gemcitabine is included in either one or more experimental arms.

A. Gemcitabine with carboplatin against either carboplatin alone or with another drug (like paclitaxel or PLD)
B. Gemcitabine against other non-platinum agent
C. Gemcitabine with other agent(s) against gemcitabine alone or with placebo.
D. Gemcitabine with other agent(s) against other agent(s)
E. Gemcitabine with carboplatin against gemcitabine, carboplatin and other agents

2.1. Outcome

2.1.1. Primary outcomes

- Overall survival. Survival until death from any cause
- Progression-free survival. Survival until progression of disease

2.1.2. Secondary outcomes

- Adverse events, classified according to (CTCAE) including all reported adverse events.

2.2. Study design

A systematic search was conducted in CENTRAL, MEDLINE and EMBASE. MEDLINE covering all articles from 1990 to present and EMBASE covering 1974 to present. A search string was adapted from Lawrie et al.'s systematic review on pegylated liposomal doxorubicin for recurrent ovarian cancer [12]. The search strings can be seen in appendix 1–3. The search was performed on the 11th of April 2018 and an additional search was performed on the 31st of May 2019. We also checked references of included studies in order to identify other studies.

All titles and abstracts were downloaded based on the electronic search, and duplicates were removed. The remaining records were handled through Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org). The records were independently handled by review author Tobias Berg (TB). Exclusion was done on titles or abstracts that did not clearly meet the inclusion criteria. Full text was obtained of the remaining records and independently handled by review author TB. The full text screening was done twice by TB. Any discrepancies between the two full texts screenings were solved involving review authors Trine Jakobi Nøttrup (TJN) and Henrik Roed (HR). Reason for exclusion was documented.

2.3. Data extraction

For all included trials we extracted the following data where possible

- Author, year of publication and journal
- Country
- Study design
- Study population
  - Total number enrolled
  - Patient characteristics
  - Age
  - Previous treatment
  - Histology
  - Performance status
- Intervention details
  - Dose
  - Regime
  - Frequency
  - Number of cycles
- Risk of bias
- Outcomes
  - Overall survival
  - Progression-free survival
  - Adverse events

2.3.1. Assessment of bias

We used the assessment of bias-tool included in the Covidence tool. This is based on The Cochrane Collaboration's Risk of Bias tool from the Cochrane Handbook of Systematic Reviews of Intervention [13].

We assessed

- Selection bias
  - Sequence generation and allocation concealment
- Performance bias
  - Blinding of participants and personnel
- Detection bias
  - Blinding of assessors of outcomes
- Attrition bias
  - Incomplete outcome data.
- Reporting bias
  - Selective outcome reporting
- Other sources of bias

3. Dealing with missing data

No imputation of missing data was done.

4. Statistical analyses

For time to event data (overall survival and progression-free survival) we abstracted the hazard ratio (HR) where possible. If the HR was not presented we calculated the HR using the tool given by TF Tierney 2007 [14]. For dichotomous outcomes (adverse events) we abstracted the number of patients who experienced the given event and the total number of patients in the specific treatment arm. When similar trials were present, we pooled their results for the meta-analysis. Time to event data was pooled using the HR and the generic inverse variance tool of RevMan 5.4. Dichotomous outcomes were pooled using the relative risk (RR). A random-effects model with inverse variance was used for all meta-analyses [15]. Forest plots were constructed to provide a graphical presentation. Statistical heterogeneity was assessed in each meta-analysis using the T^2, I^2 and Chi^2 test. We regarded heterogeneity as substantial if the I^2 was greater than 50% and the T^2 was greater than zero. A P-value of less than 0.10 in the Chi^2 test was also regarded as substantial. Evidence of heterogeneity was investigated and reported if present.

5. Results

5.1. Study selection and characteristics

Fig. 1 shows the number of articles screened, assessment of eligibility and reasons for exclusion. A total of 6 studies were included in this systematic review [9,16–20].

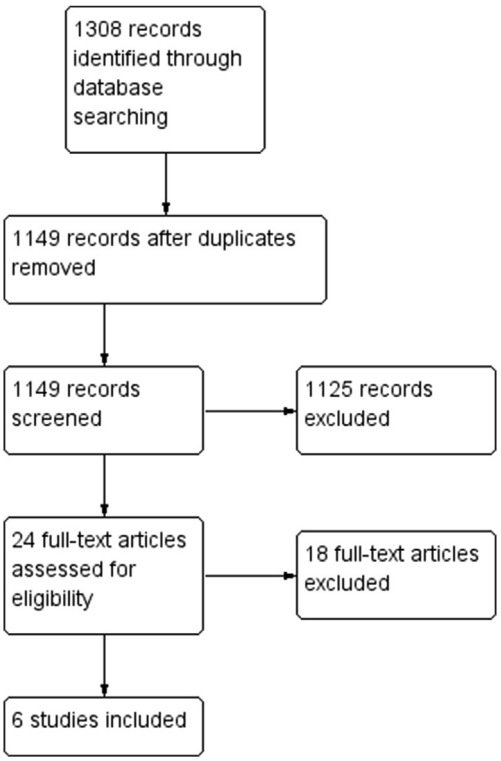

Fig. 1. Study flow diagram of searches.

All studies were randomised controlled trial. We included 1308 references of which 159 were duplicates. 1149 titles were screened based on title and abstract and we obtained the full-text on 24 records. After evaluating the full-text records we excluded 18 studies (see excluded studies) and included 6 studies.

Table 1 shows the baseline characteristics of all included studies.

5.2. Gemcitabine with carboplatin against either carboplatin alone or with another agent

We included one study in this comparison [9]. A phase III multicentre study that included 356 participants. The study compared gemcitabine and carboplatin against carboplatin. The study was conducted on women with recurrent ovarian cancer and a platinum-free interval of at least six months. Sixty percent of the patients had a platinum-free interval of more than 12 months. More than 70% of the patients had received a first-line platinum and taxane-based treatment. No prior treatment for recurrent ovarian cancer was allowed.

The primary objective was progression-free survival. Adverse events were assessed using CTCAE 1999 version 2.0. Other outcomes included overall survival, response rates and quality of life (QoL) using QLQ-C30 and QLQ-OV28 version 2.

The study showed a significantly longer progression-free survival for the combination arm compared to carboplatin alone (356 participants; HR: 0.72 95% CI; 0.72–0.89). The study showed no significant difference in overall survival between combination therapy and carboplatin alone (356 participants; HR: 0.96 95% CI; 0.75–1.23). The combination treatment was generally less well tolerated than carboplatin alone with more anaemia, neutropenia, thrombocytopenia, alopecia, diarrhoea and vomiting in the experimental arm.

5.3. Gemcitabine versus other non-platinum agent

We included two studies in this comparison [16,21]. Both studies were multicentre phase III studies randomising 153 and 195 patients, respectively. Both studies compared gemcitabine to pegylated liposomal doxorubicine.

The Ferrandina trial included women who relapsed after first-line treatment with platinum and paclitaxel within 12 months. Fifty-five percent of the patients had a platinum-free interval of less than six months. Mutch included patients with a platinum-free interval of less than 6 months and a maximum of two prior regimens were allowed. Forty percent in the gemcitabine arm had received two prior treatments. All patients had received platinum and 99% had received taxane at some point. Age and performance status in these studies were similar.

The primary outcome in Ferrandina's trial was time to progression and in Mutch's progression-free survival. Both studies had secondary outcomes of overall survival, response rates, adverse events and QoL.

There was no difference in progression-free survival between gemcitabine and PLD in the meta-analysis (2 studies; 365 participants; HR: 0.95, 95% CI; 0.75–1.21; $I^2 = 0\%$ p-value = 0.69) (Fig. 2).

There was no difference in overall survival between gemcitabine and PLD in the meta-analysis (2 studies; 365 participants: HR: 0.91 95% CI; 0.72–1.14; $I^2 = 0\%$ p-value = 0.41) (Fig. 3).

Women receiving gemcitabine were significantly more likely than women receiving PLD to experience grade 3–4 neutropenia (338 participants; risk ratio (RR) 2.25 95% CI; 1.46–3.47; I^2=0%, p-value = 0.0002) (appendix 4) Women receiving gemcitabine were significantly less likely than women receiving PLD to experience grade 3–4 hand-foot syndrome (338, risk ratio (RR) 0.07, 95% CI; 0.01–0.54, I^2=0%, p-value = 0.01) (appendix 5).

Table 1
Characteristics of included studies. G: Gemcitabine, C: Carboplatin, PLD: pegylated liposomal doxorubicin, Bev: Bevacizumab, T: Topotecan, D: day, P: Pertuzumab.

Comparison	Study	Experimental arm (n)	Control arm (n)	Experimental arm	Control arm	HR overall survival (95% CI)	HR progression-free survival (95% CI)
A	Pfisterer 2006	178	178	G: 1000mg/m2 D1 & 8 C: AUC4 D1	C: AUC5 D1	0.96 (0.75–1.23)	0.72 (0.72–0.89)
B	Ferrandina 2008	76	77	G: 1000mg/m2 D1, 8 & 15	PLD 40mg/m2 D1	0.85 (0.62–1.17)	0.93 (0.67–1.29)
B	Mutch 2006	99	96	G: 1000mg/m2 D1 & 8	PLD 50mg/m2 D1	0.98 (0.70–1.37)	0.98 (0.70–1.37)
C	Makhija 2010	65	65	G:800mg/m2 D1 & 8 P: 420 mg D1	G: 800mg/m2 D1 & 8 Placebo	0.91 (0.58–1.43)	0.66 (0.43–1.01)
D	Aghajanian 2012	242	242	G: 1000mg/m2 D1 & 8 C: AUC4 D1 Bev: 15mg/m2 D1	G: 1000mg/m2 D1 & 8 C: AUC4 D1 Placebo	0.95 (0.77–1.17)	0.48 (0.39–0.60)
E	Sehouli 2008	147	178	G: 800mg/m2 D1, 600mg/m2 D8 Top: 0.5mg/m2 D1-5	Top: 1.25mg/m2 D1-5	1.18 (0.90–1.55)	1.11 (0.88–1.40)

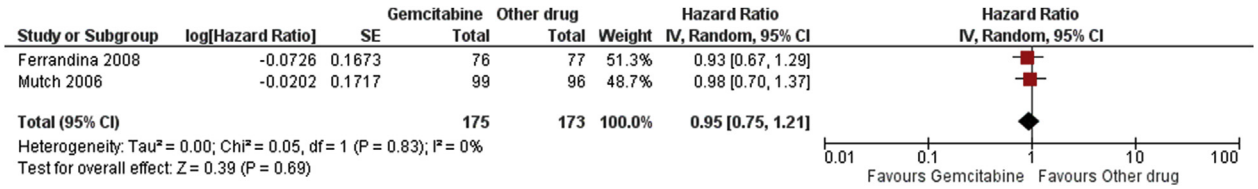

Fig. 2. Forest plot of progression-free survival for comparison B.

There were no statistically significant differences regarding anaemia, thrombocytopenia, stomatitis, vomiting and fatigue.

Meta-analysis was not possible regarding diarrhoea and sensomotory toxicity (reported in both studies, but at different grading), febrile neutropenia, dyspnoea (reported in Mutch) and leucopenia, liver and allergic reactions (reported in Ferrandina).

5.4. Gemcitabine with other agent(s) against gemcitabine alone or with placebo

We included one multicentre, randomised phase II study for this comparison [18]. The study compared gemcitabine and pertuzumab against gemcitabine and placebo.

The trial randomised 130 patients with a platinum-free interval of less than 6 months. All patients had received prior platinum-based treatment and 29 patients had received one non-platinum containing treatment prior to enrolment.

The primary outcomes were safety and progression-free survival. Secondary outcomes were objective response rate, overall survival and efficacy based on mRNA expression.

The study showed no significant difference in progression-free survival between gemcitabine and pertuzumab against gemcitabine and placebo (130 participants; HR: 0.66 95% CI; 0.43–1.03, p-value = 0.06). The study showed no significant difference in overall survival between gemcitabine and pertuzumab against gemcitabine and placebo (130 participants; HR 0.91 95% CI; 0.58–1.43, p-value = 0.68).

The study found that fewer patients experienced grade 1–2 diarrhoea and 1–2 rash in the gemcitabine alone arm. There was no difference between the two treatment arms regarding anaemia, thrombocytopenia, nausea, stomatitis, neutropenia, fatigue and arthralgia.

5.5. Gemcitabine with other agent(s) against other agent(s)

We included one multicentre, randomised phase III trial in this comparison [19]. The study compared gemcitabine, carboplatin and bevacizumab against gemcitabine, carboplatin and placebo.

The study randomised 484 patients with platinum-sensitive recurrent ovarian cancer. Platinum-sensitivity was assumed to be a platinum-free interval of more than 6 months. All patients had received prior treatment with platinum and no treatment in the recurrent setting was allowed.

The primary outcome was progression-free survival. Secondary outcomes were response rate, overall survival and adverse events.

The study showed a significantly longer progression-free survival for the experimental arm compared to the control arm (484 participants; HR: 0.48 95% CI; 0.39–0.60, p-value = <0.0001). The study showed no significant difference in overall survival between the experimental arm and the control arm (484 participants; HR 0.95 95% CI; 0.77–1.17, p-value = 0.63).

The study found that the patients in the carboplatin and gemcitabine arm experienced statistically significant less grade 1-2 stomatitis and arthralgia. There was no difference between the two arms regarding thrombocytopenia, neutropenia, febrile neutropenia, diarrhoea, nausea and fatigue.

5.6. Gemcitabine with carboplatin against gemcitabine, carboplatin and other agent(s)

We included one multicentre, randomised phase III trial in this comparison [20]. The study was a three arm study comparing topotecan to topotecan and gemcitabine or topotecan and etoposide. Patients randomised to topotecan and etoposide were not included in the analyses.

The study randomised 502 patients in three different arms. Patients were included with recurrent ovarian cancer and sixty percent in the experimental arm had a platinum-free interval of more than 12 months. All patients had been treated with platinum and more than 85% had been treated with a taxane.

The primary outcome was overall survival. Secondary outcomes were progression-free survival, response rates, adverse events and QoL.

The study showed no difference in progression-free survival for the combination arm compared to the control arm (325 participants; HR: 1.11 95% CI; 0.88–1.40, p-value = 0.38). The study showed no difference in overall survival for the combination arm compared to the control arm (325 participants; HR: 1.18 95% CI; 0.90–1.55, p-value = 0.23).

The study found that participants receiving gemcitabine with topotecan experienced more leucopenia and alopecia, where patients who only received topotecan experienced more thrombocytopenia. There was no difference between the two regarding anaemia, febrile neutropenia, diarrhoea, constipation, nausea, sensomotory toxicity and vomiting.

5.7. Risk of bias in included studies

See Fig. 4 for authors' judgement of risk of bias for each included study.

All studies included were multicentre trials with central randomisation and allocation and therefore deemed at a low risk of bias.

Aghajanian and Makhija were the only studies that were placebo controlled. The remaining four (Ferrandina, Mutch, Pfisterer and Sehouli) were all open-label and therefore at a high-risk of performance bias. Only three studies (Aghajanian, Ferrandina and Sehouli) reported methods to minimise detection bias by assessor blinding or independent review.

Attrition rates were low in all included studies for primary outcomes.

All of the included studies reported their; to our knowledge; pre-specified outcomes.

The Makhija study has been deemed at a high-risk of bias due to the possibility of crossover. The patients were allowed to crossover to 17 cycles of pertuzumab every third week for up to a year if they were randomly assigned placebo and had evidence of progression. There is no report on the number of patients who crossed-over.

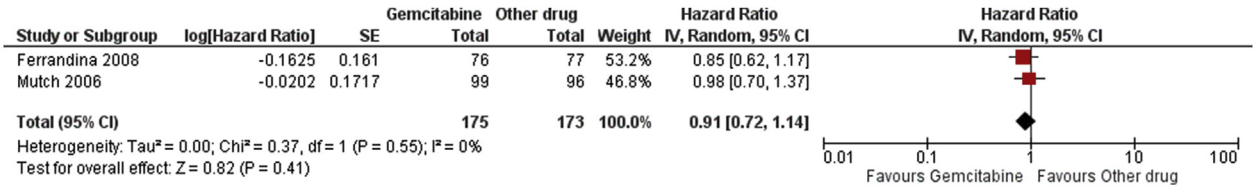

Fig. 3. Forest plot of overall survival for comparison B.

Mutch's study was designed so the patients had the option of crossing over to the opposite treatment at progression. Cross-over treatment was given to 130 patients with 66 patients receiving gemcitabine (randomised to PLD) and 64 receiving PLD (randomised to gemcitabine).

5.8. Excluded studies

We excluded five studies because they were not RCTs [22–26]. One RCT was excluded due to methodological reasons because the randomisation was based on infusion speed [27]. Twelve studies were excluded due to lack of data on gemcitabine specific outcomes [28–39].

6. Discussion

We included six randomised controlled studies that evaluated the efficacy of gemcitabine for recurrent ovarian cancer in five different comparisons. Meta-analysis was only applicable for comparison B, gemcitabine versus other non-platinum agent. We included two studies in this comparison which showed similar progression-free survival and overall survival. Gemcitabine was associated with more neutropenia, but PLD was more associated with hand-foot syndrome.

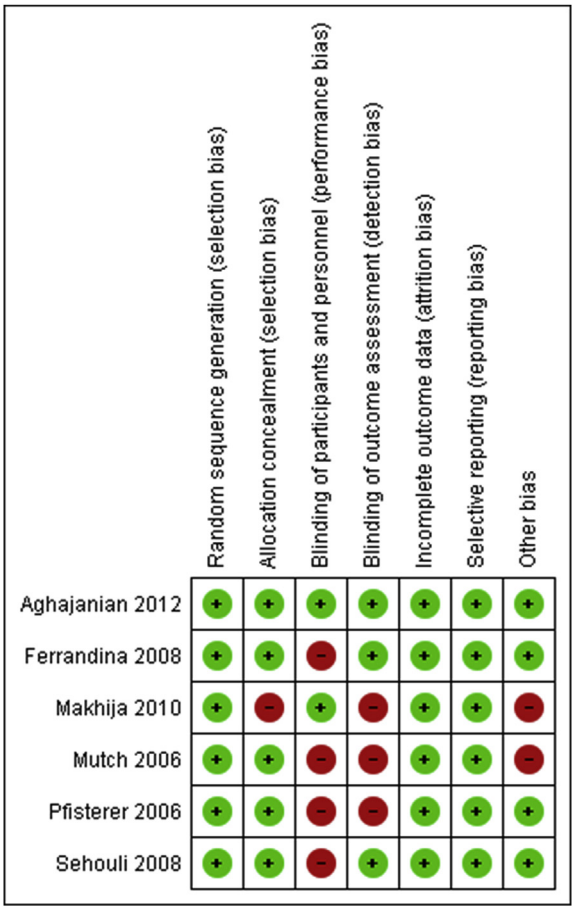

Fig. 4. Risk of bias for included studies.

There are several strengths to our systematic review. The screening and selection were systematic and conducted following the PRISMA guidelines. We included all original articles that randomised between gemcitabine and any other agent. Another strength is that we only included randomised controlled trials. This is to our knowledge the first systematic review and meta-analysis to examine the efficacy and safety of gemcitabine in recurrent ovarian cancer to date.

A limitation to the strength of the evidence of gemcitabine is the relatively low number of studies included in this systematic review. Gemcitabine in the everyday clinical practise is often used either in combination with carboplatin or as single agent therapy. The inclusion criteria of Pfisterer are similar to how patients are assigned to carboplatin and gemcitabine today. However, the most used first-line treatment of platinum-sensitive recurrent ovarian cancer is carboplatin and PLD. Pfisterer compared carboplatin and gemcitabine to carboplatin alone. There is no randomised trial that has compared carboplatin and gemcitabine to carboplatin and PLD, but there is a systematic review from 2010 that found comparable response rates and toxicities between the two [40].

When gemcitabine is used in the everyday clinical practise as single agent therapy, it is often used for heavily pre-treated patients. Current NCCN Guidelines® and ESMO-ESGO guidelines do not describe an optimal treatment sequence for systemic treatment for recurrent disease, but patients are often challenged with PLD and paclitaxel before being exposed to gemcitabine [4,7]. The Ferrandina trial included women who experienced progression on first-line treatment with carboplatin and paclitaxel within 12 months. Forty-five percent of the patients had a platinum-free interval of more than six months and would most likely be retreated with a platinum-containing treatment regime today. In Mutch's trial the patients had to be platinum resistant with a platinum-free interval of less than six months but were only allowed to have had received a maximum of two prior treatments for recurrent ovarian cancer. This could indicate that the patient population in which we use gemcitabine today is different than that we base our evidence on. The observed differences in hand-foot syndrome and hand-foot syndrome (RR; 0.07, 95% CI 0.01–0.54) was expected due to PLD-induced skin toxicity whereas the difference in neutropenia (neutropenia, RR; 2.25 95% CI 1.46–3.47) can be explained by gemcitabine's haematologic toxicity [8].

7. Conclusion

In conclusion, gemcitabine is an active agent in recurrent ovarian cancer. In combination with carboplatin for platinum-sensitive disease it shows a significant better progression-free survival than mono-therapeutic carboplatin. However, there is no difference in overall survival. As single agent therapy, gemcitabine shows similar progression-free survival and overall survival as PLD.

The evidence for single agent gemcitabine for platinum-resistant recurrent ovarian cancer does not necessarily reflect the way it is used in everyday clinical practise and could warrant the need of a randomised trial in heavily pre-treated patients.

Author contributions

All authors contributed to the design of the review. TB completed the initial data search. All authors approved the final approved trials. TB wrote the first manuscript draft and all authors approved the final manuscript.

Declaration of competing interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.09.026.

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