Tolerability, efficacy, and safety of pegylated liposomal doxorubicin in combination with carboplatin versus gemcitabine-carboplatin for the treatment of platinum-sensitive recurrent ovarian cancer: a systematic review
Holloway RW, Grendys EC, Lefebvre P, Vekeman F, Mcmeekin S

CRD summary
This review concluded that pegylated liposomal doxorubicin in combination with carboplatin therapy was a rational alternative to gemcitabine-carboplatin for treatment of patients with platinum-sensitive recurrent ovarian cancer. These conclusions should be interpreted with caution due to the limited methodological rigour of the included studies, some concerns in the review methods and the possibility of publication bias.

Authors' objectives
To compare the efficacy, safety and tolerability of pegylated liposomal doxorubicin in combination with carboplatin (PLD-Carboplatin) versus those of gemcitabine-carboplatin (Gem-Carboplatin) for the treatment of platinum-sensitive recurrent ovarian cancer.

Searching
PubMed was searched for published peer-reviewed studies between January 2000 and September 2009. There were no language restrictions. Search terms were reported. Reference lists of relevant publications were screened.

Study selection
Studies that evaluated PLD-Carboplatin or Gem-Carboplatin and reported response rate, progression-free survival and/or overall survival in patients with platinum-sensitive recurrent ovarian cancer were eligible for inclusion. Studies reported in non-English languages were included if the relevant data were available in the abstract.

Most of the included studies were phase II trials. Of the included studies, the mean target carboplatin areas under the curve (AUC) were 5.2 for the PLD-Carboplatin group and 4.3 for the Gem-Carboplatin group. The mean planned dose was 34.8mg/m² for pegylated liposomal doxorubicin and 993mg/m² for gemcitabine. Median age of patients was 60 years for the PLD-Carboplatin group and 59 years for the Gem-Carboplatin group. Three different definitions were used for response rate in the included studies. The treatment groups had similar Eastern Cooperative Oncology Group performance status scores.

Two reviewers independently assessed studies for inclusion.

Assessment of study quality
The authors did not state they assessed validity.

Data extraction
The number of patients who experienced an event and time to event data were extracted. Where relevant data were only reported graphically, data were estimated from the graphs.

Two reviewers independently performed data extraction. Any disagreement was resolved by a third reviewer.

Methods of synthesis
The pooled median progression-free survival and overall survival were calculated by weighting the number of evaluable patients in each study. The weighted average of response rate and percentages of adverse events were calculated.

Results of the review
Ten studies (n=608 patients) were included in the review: five studies of PLD-Carboplatin (n=278) and five studies of Gem-Carboplatin (n=330). Sample size ranged from 26 to 178. Only two studies were randomised. The other trials
were open-label or non-randomised.

The proportion of patients who received PLD-Carboplatin and achieved a response was 60.2% (27.0% achieved complete response and 33.2% achieved partial response) and the proportion of patients who received Gem-Carboplatin and achieved a response was 51.4% (19.2% achieved complete response and 32.2% achieved partial response).

Median progression-free survival time was 10.6 months for the PLD-Carboplatin group and 8.9 months for the Gem-Carboplatin group. Median overall survival was longer for the PLD-Carboplatin group than the Gem-Carboplatin group (27.1 months versus 19.7 months).

The dose intensity reported in Gem-Carboplatin trials was lower than that in PLD-Carboplatin trials (75% of the planned dose versus 93.7% of the planned dose), which indicated better tolerability for the PLD-Carboplatin regimen.

Grade III or IV anaemia (PLD-Carboplatin 13.6% versus Gem-Carboplatin 24.5%) and neutropenia (PLD-Carboplatin 45.5% versus Gem-Carboplatin 62.9%) were more common in patients who received Gem-Carboplatin. Haematological safety profiles were comparable between the two groups.

Authors’ conclusions
Pegylated liposomal doxorubicin in combination with carboplatin therapy was a rational alternative to gemcitabine-carboplatin for treatment of patients with platinum-sensitive recurrent ovarian cancer.

CRD commentary
This review’s inclusion criteria were clear. Only one database was searched, so some potentially relevant studies may have been missed. No attempts were made to find unpublished studies, which increased potential for publication bias. No language restrictions were applied to the search, which minimised the possibility of language bias. Steps were taken to minimise errors and biases in the processes of study selection and data extraction. No formal validity assessment was performed. Most of the included studies had a non-randomised open-label design (a study design was of low methodological rigour). The pooled results were calculated by weighting the number of evaluable patients in each study. It was unclear whether statistical heterogeneity was assessed. Given the level of clinical heterogeneity between included studies (such as study design), pooling the results to derive a single measure might not have been appropriate.

The authors’ conclusions should be interpreted with caution, given the limited methodological rigour of included studies, some concerns in the review methods and the possibility of publication bias.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that a phase III randomised controlled trial was required to evaluate the relevant efficacy and safety profile of PLD-Carboplatin versus Gem-Carboplatin for treatment of platinum-sensitive recurrent ovarian cancer.

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