Randomized evidence on chemotherapy and hormonal therapy regimens for advanced endometrial cancer: an overview of survival data

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CRD summary
This review evaluated chemotherapy and hormonal regimens for the treatment of advanced endometrial cancer. The authors concluded that the available evidence was limited and relatively weak. Overall, this was a well-conducted review and the authors’ conclusions appear appropriate.

Authors' objectives
To evaluate chemotherapy and hormonal regimens for the treatment of advanced endometrial cancer.

Searching
MEDLINE, EMBASE and the Cochrane CENTRAL Register were searched to April 2005; some search terms were reported. The authors stated that the full search strategy is available on request. The reference lists of previous reviews of RCTs were screened and cross-searches were conducted in MEDLINE using the names of lead authors in eligible trials. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with at least 5 patients per treatment arm were eligible for inclusion. Pseudo-randomised trials that used alternate allocation were excluded.

Specific interventions included in the review
Studies that compared at least two different chemotherapy or hormonal therapy regimens were eligible for inclusion. The studies could compare different dosing regimens and schedules of the same agent, or use combinations of agents. The authors also noted any trials that compared chemotherapy or hormonal therapy with best supportive care alone. The included studies compared a variety of different monotherapy and combination regimens. Combination regimens contained two or more chemotherapy agents or hormonal plus chemotherapy agents (seven monotherapy regimens and fourteen combinations of different agents). The most commonly used hormonal regimen was medroxyprogesterone acetate and the most commonly used chemotherapy regimen was cisplatin plus doxorubicin; other chemotherapy regimens used in more than one trial were doxorubicin monotherapy and cyclophosphamide monotherapy. Studies compared monotherapy with combination therapy, different monotherapies, and different combination regimens. Details of all the included interventions were reported.

Participants included in the review
Studies of patients with advanced endometrial cancer (stage IIIB or IV, unresectable or recurrent) were eligible for inclusion. Studies that only included patients with non-advanced disease or cancer of the uterine cervix were excluded. For studies that included some patients with non-advanced disease, the review focused on relevant subgroups. The included studies differed in the proportion of women with performance status of 2 or worse (8 to 50% in 12 studies), the proportion with stage IV disease (9 to 86% in 6 studies), and the proportion who had received systemic therapy (9 studies allowed previous hormonal therapy and few studies allowed previous chemotherapy) or radiotherapy (44 to 83% in 11 studies) previously.

Outcomes assessed in the review
Inclusion criteria for the outcomes were not explicitly reported, but it was clear that the review focused on median survival.

How were decisions on the relevance of primary studies made?
The authors did not state how the studies were selected for the review, or how many reviewers performed the selection.
Assessment of study quality
The studies were assessed for blinding, adequate reporting of the randomisation method, allocation concealment and method of survival analysis (strict intention-to-treat). Two reviewers assessed validity and resolved any disagreements through consensus.

Data extraction
Two reviewers extracted the data and resolved any disagreements through consensus. The number of patients considered eligible and the number randomised, the median survival with each treatment, and the level of statistical significance for the comparison between treatments were extracted from each study. The results for the log rank test and unadjusted analyses were extracted preferentially where studies reported different analyses. Reports of survival differences were examined to determine the underlying analyses.

Methods of synthesis
How were the studies combined?
The studies were grouped by interventions compared and combined in a narrative.

How were differences between studies investigated?
Differences between the studies were discussed with respect to interventions compared. The correlation was estimated between the year of publication and percentage of patients with performance status 2 or worse, sample size and the proportion of patients with stage IV disease. Univariate and multivariate regression analyses were used to examine the relationship between median survival and sample size, percentage of patients with poor performance status and decade of study.

Results of the review
Seventeen RCTs (n=2,961) were included.

Three RCTs adequately described an appropriate method of randomisation and 8 RCTs adequately described appropriate allocation concealment. Four RCTs reported strict intention-to-treat analysis. None of the RCTs could be blinded.

Only four regimens were evaluated in more than one trial and only two of the trials used the same comparison regimen.

Only one trial reported a statistically significant difference in median survival for an adjusted analysis of doxorubicin plus cisplatin versus the combination doxorubicin-cisplatin-paclitaxel-granulocyte colony stimulating factor: 12.3 months versus 15.3 months (p=0.032). Three other trials reported survival difference for specific secondary analyses; one of these trials reported poorer survival with the experimental treatment. Differences in survival between treatments were small, with most differences being less than 3.5 months.

More recent studies tended to include a lower proportion of patients with poor performance status (p=0.001) and tended to be larger (p=0.019).

Univariate analyses showed that median survival was statistically significantly associated with the proportion of patients with poor performance status (p<0.001) but not with sample size (p=0.060). The analyses also showed that survival significantly improved over time (1.6 months per decade, p=0.016), although this was explained by the increased proportion of patients with poor performance status in earlier studies. The multivariate analysis showed poorer survival in studies with an increased proportion of patients with performance status 2 or worse (-2.3 months per 10% increase in the proportion of poor status patients, p<0.001), but no improved survival in more recent studies (p=0.99) and no significant association between survival and sample size (p=0.89).

Authors' conclusions
Evidence about hormonal and chemotherapy regimens for women with advanced endometrial cancer was limited and relatively weak.

**CRD commentary**
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Three databases were searched and some attempts were made to minimise publication and language bias. Methods were used to minimise reviewer errors and bias in the assessment of validity and extraction of data, but it was unclear whether similar steps were taken when selecting the studies. Validity was assessed using specified criteria and the results of this assessment were reported. Adequate information about the individual studies was presented. Given the differences between the studies, the methods used to combine the studies were appropriate. Differences between the studies were discussed and the influence of various factors on survival was examined. Overall this was a well-conducted review and the authors’ conclusions highlight the limitations of the evidence.

**Implications of the review for practice and research**
The authors did not state any implications for practice or further research.

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