Chemotherapy for advanced, recurrent or metastatic endometrial cancer: a systematic review of Cochrane collaboration

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Background: Cytotoxic chemotherapy has a limited place in the management of advanced or recurrent endometrial cancer. Commonly used agents include cisplatin and doxorubicin, but the side-effect profile may be unacceptable for many patients. The feasibility of administration of combination chemotherapy is limited in many patients on account of significant co-morbidity. While early-stage endometrial adenocarcinoma is a common gynaecological cancer with a favourable prognosis, advanced or recurrent disease presents a difficult management problem. The platinum and anthracycline compounds have been widely used for many years, but their impact on progression-free survival (PFS) and overall survival (OS) is not clear. This systematic review aimed to evaluate both the benefits and adverse effects of cytotoxic chemotherapy in these women.

Patients and methods: We carried out systematic searches for randomised controlled trials (RCTs) comparing chemotherapy with another intervention. Data were extracted from trial reports or supplied by investigators. Where possible, hazard ratios (HRs) were calculated for OS and PFS and odds ratios (ORs) were calculated for acute toxicity. The impact of more versus less intensive chemotherapy on OS, PFS and acute toxicity was assessed in a meta-analysis.

Results: Eleven eligible RCTs were identified that recruited 2288 patients. A meta-analysis of six of these trials found that PFS [HR = 0.80, 95% confidence interval (CI) 0.71–0.90; P = 0.004], but not OS (HR = 0.90, 95% CI 0.80–1.03; P = 0.12), was significantly improved when more intensive chemotherapy was compared with less intensive chemotherapy. OS was improved when doxorubicin, cisplatin and other drugs were compared with doxorubicin and cisplatin. Toxicity was generally higher with more chemotherapy. There was insufficient evidence to assess the effect of chemotherapy on symptom control or quality of life (QoL). Platinums, anthracyclines and taxanes were the most studied in phase II trials and combinations gave the best responses, but patient selection and pre-treatment was very variable.

Conclusions: More intense combination chemotherapy significantly improves the disease-free survival and the data indicate a modest improvement in OS. The addition of anthracyclines (e.g. doxorubicin) or the taxanes [e.g. paclitaxel (Taxol)] to cisplatin increases the response rate. More intensive regimens are associated with the gain in survival. However, grade 3 and 4 myelosuppression and gastrointestinal toxicity are also increased. Future developments are likely to exploit specific molecular characteristics of endometrial cancers, including their hormone dependence, growth factor target overexpression and PTEN loss. While no one drug or regimen offers a clear benefit for women with advanced endometrial cancer, platinum drugs, anthracyclines and paclitaxel seem the most promising agents. Future trials should address the impact of such agents on QoL and symptom control in addition to survival. Chemotherapy and endocrine therapy need to be compared directly in an RCT.

Key words: cytotoxic chemotherapy, endometrial cancer, meta-analysis, randomized controlled trials, review

There were ~200 000 cases of endometrial adenocarcinoma worldwide in 2005 with ~50 000 deaths [1]. There is, however, wide geographical variation in disease incidence with the
highest in North America (22.0 per 100 000 per year) and Europe (11.8–12.5 per 100 000 per year) [1].

Most women present with early disease and are treated with surgery, giving 5-year survival rates of >70\%. Women with certain histological subtypes, high-grade lesions, deep invasion of the uterus, tumour extending to the cervix, spread to lymphatic or blood vessels or outside the uterus are at high risk of recurrence [2] and may be offered adjuvant radiotherapy. Only a small proportion of women present with advanced disease at diagnosis. If the tumour is not amenable to surgery or radical radiotherapy, then women are considered for systemic endocrine therapy or cytotoxic chemotherapy, with the aim of palliating symptoms, improving quality of life (QoL), delaying progression of disease and extending overall survival (OS). Moreover, many patients with endometrial cancer are obese with significant co-morbidity such as diabetes mellitus and ischaemic heart disease, which can restrict treatment options.

Cytotoxic chemotherapy has been used for advanced disease. Commonly used regimens incorporate the platinum agents and anthracyclines, on the basis of phase II and limited phase III data. Cross-resistance between the taxanes and anthracyclines, however, is also incomplete in many tumour types in vitro and phase II studies.

Early studies used single agents with modest response rates and remission durations of 4–6 months were seen. Combinations of two or more drugs have been employed, but the general perception is that these patients tolerate chemotherapy less well than comparable patients with breast or ovarian cancers. Furthermore, cross-resistance between different groups of agents is common and responses in chemotherapy-pre-treated patients are low. Debate over the role of pelvic radiotherapy has further complicated the use of chemotherapy as prior radiotherapy compromises both the activity and assessment of subsequent chemotherapy.

The aim of this review is to evaluate the impact of cytotoxic chemotherapy on progression-free survival (PFS), OS, QoL and symptom relief, as well as to assess the toxicity of such treatment.

**patients and methods**

Randomised controlled trials (RCTs) were sought by a systematic search of major bibliographic databases, trial registers and by hand searching the reference lists of studies identified. The amount of randomised evidence found was limited and so we extended our searches to include non-randomised phase II studies of the response to chemotherapy updated at the end of 2005.

For the meta-analysis, only RCTs that compared cytotoxic chemotherapy (single agent or combination) versus placebo, best supportive care, alternative chemotherapy or endocrine (hormonal) therapy were considered. They should have aimed to randomly assign women with advanced, recurrent or metastatic endometrial adenocarcinoma that was not amenable to potentially curative surgery or radical radiotherapy. Trials of adjuvant chemotherapy or which included women with uterine carcinosarcoma or sarcoma were excluded.

Data on trial design, participants, treatments, relevant outcomes and analyses were extracted from the reports of each included trial by two authors independently. The outcomes of interest were OS, PFS, QoL measured on a validated QoL instrument, acute and late toxicity grade on a validated scoring system and any measure of symptom control. OS and PFS were considered the primary outcomes. Authors were contacted for extra information and updated outcome data.

Meta-analyses of single-agent chemotherapy versus the same drug in combination, and two-drug chemotherapy versus the same two drugs in combination with other drugs were considered feasible and are combined to give an overall comparison of more versus less chemotherapy.

Hazard ratios (HRs) were used directly in meta-analyses if provided in the trial report or by the investigators. Where they were not provided, they were estimated indirectly from other summary statistics or from the data extracted from published Kaplan–Meier curves [3]. These were then combined across all trials using the fixed-effect model to give a pooled HR [4], which represents the overall risk of an event on the research treatment versus control. Absolute differences in median PFS and OS were estimated using the HR and average median control group PFS and OS [(median/HR) – median].

Scales, grades and sites of acute toxicity were extracted from the text and grouped into common subtypes: nausea and vomiting, diarrhoea/other gastrointestinal (GI), leucopenia, thrombocytopenia, fever/infection, renal/genitourinary, neurological, alopecia, anaemia, cardiotoxicity, fever/infection and stomatitis/mucositis. A meta-analysis was carried out to compare the toxicity of less versus more chemotherapy using odds ratios (ORs) to calculate the total number of grade 3 and 4 events for each subtype. Where more than one type of toxicity was reported in a category (e.g. nausea reported separately from vomiting), the most frequent was used. These ORs were combined across all trials, using the fixed-effect model, to give the odds of any toxic event or severe toxic event for each type of toxicity in the treatment arm (more chemotherapy) versus the control arm (less chemotherapy). Differences between trial results were assessed using the $I^2$ for inconsistency [5], which gives values between 0% and 100%. Low values (~25%) indicated a low level of inconsistency, high values (~75%) a high level of inconsistency and intermediate values (~50%) moderate level of inconsistency. All $P$ values quoted are two-sided.

**results**

**RCTs of chemotherapy**

Eleven eligible RCTs were identified. All trials compared one form of chemotherapy with another. No trials compared chemotherapy with best supportive care or hormone therapy. Of these reports, three gave only limited data on the primary end points of PFS and OS [6–8]. The toxicity scales used varied from trial to trial, but grouping of toxicity data as described in the Materials and methods section was feasible. No trials collected QoL data or objective measures of symptoms. Further information was requested from all authors but updated data were only obtained for three trials [7, 9, 10]. Characteristics of the included trials are given in Table 1.

Only four trials gave details of the method of randomisation [10–13], although some details of stratification were given for three others [6, 9, 14]. Five reports indicated that randomisation was carried out by a central office [6, 12, 13, 15, 16]. Six studies described how the sample size was determined [8, 10, 12, 13, 15, 16]. Three trials randomly assigned <50 patients [6, 7, 9] and because of this would only be sufficiently powered to detect a very large difference in the effectiveness of the two arms. Two studies were stopped prematurely [7, 10].

Eight of 11 eligible trials excluded patients after randomisation [6, 8, 11–16] mainly for reasons of ineligibility or because they were deemed inassessable. Sometimes, more patients were excluded from one arm than the other, as shown...
**Table 1.** Characteristics of randomised controlled trials of chemotherapy

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Accrual period</th>
<th>Patients randomly assigned (and excluded)</th>
<th>Chemotherapy</th>
<th>Overall response rate (%)</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edmonson et al. [7]</td>
<td>1980–1983</td>
<td>30 (no patients excluded)</td>
<td>Arm 1: cisplatin 60 mg/m² i.v. every 21 days until progression Arm 2: cyclophosphamide 400 mg/m² i.v., doxorubicin 40 mg/m² i.v., cisplatin 40 mg/m² i.v., cisplatin every 28 days until progression</td>
<td>Arm 1: 21</td>
<td>Arm 1: 1.8</td>
<td>Arm 1: 4.1</td>
</tr>
<tr>
<td>Aapro et al. [8]</td>
<td>1988–1994</td>
<td>177 (12 patients ineligible and five without follow-up data, but all patients analysed for efficacy; 12 patients receiving one cycle of chemotherapy excluded from toxicity analyses)</td>
<td>Arm 1: doxorubicin 60 mg/m² i.v. every 28 days Arm 2: doxorubicin 60 mg/m² i.v., cisplatin 50 mg/m² i.v. every 28 days</td>
<td>Arm 1: 17</td>
<td>Arm 1: 7</td>
<td>Arm 1: 7</td>
</tr>
<tr>
<td>Thigpen et al. [9]</td>
<td>1979–1985</td>
<td>387 (31 ineligible patients excluded from the analyses due to ineligibility; 80 more patients not assessable for response)</td>
<td>Arm 1: doxorubicin 60 mg/m² i.v. every 21 days Arm 2: doxorubicin 60 mg/m² i.v., cyclophosphamide 500 mg/m² i.v. every 21 days</td>
<td>Arm 1: 22</td>
<td>Arm 1: 3.2</td>
<td>Arm 1: 6.9</td>
</tr>
<tr>
<td>Thigpen et al. [14]</td>
<td>1988–1992</td>
<td>299 (18 ineligible patients excluded from the analyses due to ineligibility, uncertain eligibility or inadequate; three more patients not receiving chemotherapy excluded from toxicity analyses)</td>
<td>Arm 1: doxorubicin 60 mg/m² i.v. every 21 days Arm 2: doxorubicin 60 mg/m², cisplatin 50 mg/m² i.v. every 21 days</td>
<td>Arm 1: 25</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td>Long et al. [5]</td>
<td>Not stated</td>
<td>28 (no patients excluded)</td>
<td>Arm 1: doxorubicin plus cyclophosphamide every 28 days until progression Arm 2: methotrexate, vinblastine, doxorubicin, cisplatin every 28 days until progression</td>
<td>Arm 1: 27</td>
<td>Arm 1: 6.2</td>
<td>Arm 1: 15</td>
</tr>
<tr>
<td>Fleming et al. [13]</td>
<td>1998–2000</td>
<td>273 (10 patients excluded from analyses due to ineligibility; three more patients receiving one cycle of chemotherapy excluded from toxicity analysis)</td>
<td>Arm 1: doxorubicin 60 mg/m² i.v., cisplatin 50 mg/m² i.v. every 21 days for seven cycles Arm 2: doxorubicin 45 mg/m² i.v., cisplatin 50 mg/m² i.v., paclitaxel 160 mg/m² i.v. every 21 days for seven cycles plus G-CSF support</td>
<td>Arm 1: 34</td>
<td>Arm 1: 5.3</td>
<td>Arm 1: 12.3</td>
</tr>
<tr>
<td>Horton et al. [4]</td>
<td>Not stated</td>
<td>47 (seven patients excluded from analyses due to protocol violations or unavailability of data)</td>
<td>Arm 1: doxorubicin 50 mg/m² i.v. bolus every 21 days until progression Arm 2: cyclophosphamide 666 mg/m² i.v. bolus every 21 days until progression</td>
<td>Arm 1: 19</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Pawinski et al. [6]</td>
<td>1987–1994</td>
<td>74 (13 ineligible patients excluded from analysis due to of ineligibility; patients dying of non-malignant disease before evaluation were considered inassessable)</td>
<td>Arm 1: cyclophosphamide 1200 mg/m² i.v. infusion every 21 days until progression Arm 2: ifosfamide 5 g/m² i.v. Infusion every 21 days until progression</td>
<td>Arm 1: 7</td>
<td>Arm 1: 1.6</td>
<td>NR</td>
</tr>
</tbody>
</table>

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in Table 1. There was variability in statistical analysis between these studies, with some providing much clearer definitions of outcomes and information on how the analysis was carried out than others and the duration of follow-up was not always well documented.

**meta-analysis of RCTs of more versus less intense chemotherapy**

Four trials were identified that compared a single agent with the same agent in combination [9–11, 16] (Table 1). Two further trials compared doxorubicin and cisplatin with doxorubicin and cisplatin combined with other drugs [7, 15] (Table 1). The reported response rates, median PFS and median OS for each trial are listed in Table 1. Six trials were included in the meta-analysis of less chemotherapy versus more chemotherapy [7, 9–11, 15, 16]. Despite the exclusion of patients, the trials of more versus less chemotherapy were well balanced with respect to well-known prognostic factors such as age, stage and performance status. In the study of cyclophosphamide, doxorubicin and cisplatin (CAP) versus cisplatin [9], however, a slightly higher proportion had received prior radiation in the CAP arm. In another trial of doxorubicin and cyclophosphamide versus doxorubicin [11], there was a higher proportion of patients with grade 3 tumours in the doxorubicin arm. In all six trials, the objective response rate (ORR) appeared greater when more was compared with less chemotherapy (30%–69% versus 17%–34%, Table 2). These differences were statistically significant in only two of the trials [15, 16].

Progression data were available for these six trials (1132 patients and 1014 events), although only as time to progression in two of these [7, 10]. Across all included trials, the results show a moderate degree of consistency, irrespective of the regimens being compared ($I^2 = 38.9\%$), and overall, the results favoured more rather than less chemotherapy. The pooled HR of 0.80 [95% confidence interval (CI) 0.71–0.90] shows a highly significant 20% relative improvement in PFS ($P = 0.0004$) with more intensive regimens (Figure 1) which translates into an absolute improvement in the median PFS of $\sim 1$ month.

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Accrual period</th>
<th>Patients randomly assigned (and excluded)</th>
<th>Chemotherapy</th>
<th>Overall response rate (%)</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
</table>
| Fleming et al. [11] | 1996–1998 | 328 (11 patients excluded from the analyses due to ineligibility or withdrawn patient consent; four more receiving less than one cycle of chemotherapy excluded from toxicity analyses) | Arm 1: doxorubicin 60 mg/m$^2$ i.v., cisplatin 50 mg/m$^2$ i.v. every 21 days for seven cycles or until progression or unacceptable toxicity  
Arm 2: doxorubicin 50 mg/m$^2$ i.v., paclitaxel 150 mg/m$^2$ i.v., filgrastim 5 mcg/kg d3-12 every 21 days for seven cycles or until progression or unacceptable toxicity | Arm 1: 40  
Arm 2: 43 | Arm 1: 7.2  
Arm 2: 6.0 | Arm 1: 12.6  
Arm 2: 13.6 |
| Gallion et al. [10] | 1993–1996 | 352 (10 patients excluded from the analyses because of ineligibility) | Arm 1: doxorubicin 60 mg/m$^2$ i.v., cisplatin 60 mg/m$^2$ i.v. every 21 days for eight cycles  
Arm 2: doxorubicin 60 mg/m$^2$ i.v. at 6 am, cisplatin 60 mg/m$^2$ i.v. at 6 pm every 21 days for eight cycles | Arm 1: 46  
Arm 2: 49 | Arm 1: 6.5  
Arm 2: 5.9 | Arm 1: 11.2  
Arm 2: 13.2 |
| Cohen et al. [12] | 1977–1979 | 295 (25 patients excluded from analysis due to ineligibility and 13 excluded because they were inassessable) | Arm 1: melphalan 7 mg/m$^2$/day p.o. for 4 days, 5-FU 525 mg/m$^2$/day i.v. for 4 days repeated every 28 days, megace 180 mg/day orally for 8 weeks  
Arm 2: doxorubicin 40 mg/m$^2$ i.v. bolus, cyclophosphamide 400 mg/m$^2$ i.v. bolus, 5-FU 400 mg/m$^2$ i.v. bolus every 21 days plus megace as for arm 1 | Arm 1: 38  
Arm 2: 36 | Arm 1: 6.1  
Arm 2: 5.2 | Arm 1: 10.6  
Arm 2: 10.1 |

5-FU, 5-fluorouracil; G-CSF, granulocyte colony-stimulating factor; NR, not recorded; OS, overall survival; PFS, progression-free survival.
The effect is more pronounced in the group of trials that compared doxorubicin and cisplatin plus other drugs with doxorubicin and cisplatin alone [7, 15], with a HR of 0.64 (95% CI 0.49–0.82, \(P = 0.0004\)). The Fleming et al. trial [13] had an individual result that was significantly in favour of more chemotherapy, the additional drug being paclitaxel (Taxol).

Data on OS were available for six trials, including 1135 patients and 1034 events and the results of these trials of various types of chemotherapy are very consistent (\(I^2 = 18.6\%\)). There is no OS benefit for more compared with less chemotherapy (HR = 0.91, 95% CI 0.80–1.03; \(P = 0.12\)) (Figure 2). Doxorubicin and cisplatin in combination with other drugs, however, do offer a survival benefit when compared with doxorubicin and cisplatin alone [7, 15]. The HR of 0.75 (95% CI 0.58–0.97) indicates a 25% reduction in the relative risk of death with more intense chemotherapy equivalent to a 3-month improvement in survival. These results are largely driven by the results of the one trial evaluating the addition of paclitaxel [15] that individually had a statistically significant result (HR = 0.75, 95% CI 0.57–0.98; \(P = 0.037\), adjusted for performance status).

Data on grade 3 or 4 nausea and vomiting, diarrhoea/other GI toxicity, leucopenia, thrombocytopenia and neurological toxicity were available in sufficient detail for five out of six trials, including 761 patients. To assess toxicity, two trials used the National Cancer Institute Common Toxicity Criteria (CTC) [7, 9], one used the CTC criteria version 2 [15], one used the World Health Organisation (WHO) criteria [10] and two the Gynaecologic Oncology Group (GOG) criteria [11, 16]. Across

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**Table 2.** Characteristics of phase II trials of chemotherapy: cisplatin-containing regimens

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Patients recruited (and having prior chemotherapy)</th>
<th>Chemotherapy</th>
<th>Overall response rate (%)</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seski et al. [17]</td>
<td>26 (5)</td>
<td>Cisplatin 50–100 mg/m²</td>
<td>42</td>
<td>5</td>
<td>NR</td>
</tr>
<tr>
<td>Thigpen et al. [18]</td>
<td>31 (24)</td>
<td>Cisplatin 50 mg/m²</td>
<td>4</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Thigpen et al. [19]</td>
<td>56 (0)</td>
<td>Cisplatin 50 mg/m²</td>
<td>20</td>
<td>2.9</td>
<td>8.2</td>
</tr>
<tr>
<td>Barrett et al. [20]</td>
<td>33 (0)</td>
<td>Cisplatin 60 mg/m², doxorubicin 60 mg/m²</td>
<td>60</td>
<td>7.5</td>
<td>14</td>
</tr>
<tr>
<td>Deppe et al. [21]</td>
<td>19 (NR)</td>
<td>Cisplatin 50 mg/m², Doxorubicin 50 mg/m²</td>
<td>37</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Trope et al. [22]</td>
<td>19 (0)</td>
<td>Cisplatin 50 mg/m², doxorubicin 50 mg/m²</td>
<td>60</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Pasmanter et al. [23]</td>
<td>16 (4)</td>
<td>Cisplatin 60 mg/m², doxorubicin 60 mg/m²</td>
<td>81</td>
<td>NR</td>
<td>10</td>
</tr>
<tr>
<td>Lovecchio et al. [24]</td>
<td>15 (0)</td>
<td>Cisplatin 50 mg/m², doxorubicin 30 mg/m², cyclophosphamide 300 mg/m², megace 120 mg/day</td>
<td>60</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Turbow et al. [25]</td>
<td>21 (0)</td>
<td>Cisplatin 60 mg/m², doxorubicin 50 mg/m², cyclophosphamide 600 mg/m²</td>
<td>47</td>
<td>NR</td>
<td>10</td>
</tr>
<tr>
<td>Hancock et al. [26]</td>
<td>18 (0)</td>
<td>Cisplatin 50 mg/m², doxorubicin 50 mg/m², cyclophosphamide 500 mg/m²</td>
<td>56</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Hoffman 1989 [57]</td>
<td>15 (NR)</td>
<td>Cisplatin 50 mg/m², doxorubicin 30 mg/m³, cyclophosphamide 500 mg/m³, megace 160 mg/day</td>
<td>33</td>
<td>3.9</td>
<td>1.2</td>
</tr>
<tr>
<td>Burke et al. [27]</td>
<td>102 (0)</td>
<td>Cisplatin 50 mg/m², doxorubicin 50 mg/m³, cyclophosphamide 500 mg/m³</td>
<td>45</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Pietrzak et al. [28]</td>
<td>41 (NR)</td>
<td>Cisplatin 50 mg/m², doxorubicin 50 mg/m³, cyclophosphamide 500 mg/m³</td>
<td>12</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Alberts et al. [30]</td>
<td>64 (0)</td>
<td>Cisplatin 50 mg/m², doxorubicin 30 mg/m², vinblastine 0.15 mg/m²</td>
<td>31</td>
<td>NR</td>
<td>6.5</td>
</tr>
<tr>
<td>Piver et al. [31]</td>
<td>20 (2)</td>
<td>Cisplatin 60 mg/m², doxorubicin 40 mg/m², etoposide 225 mg/m³, megace 160 mg/day</td>
<td>75</td>
<td>NR</td>
<td>15</td>
</tr>
<tr>
<td>Cornelison et al. [32]</td>
<td>50 (0)</td>
<td>Cisplatin 60 mg/m², doxorubicin 40 mg/m², etoposide 225 mg/m³, megace 160 mg/day</td>
<td>54</td>
<td>11.9</td>
<td>16.4</td>
</tr>
<tr>
<td>Long et al. [33]</td>
<td>30 (0)</td>
<td>Cisplatin 70 mg/m², doxorubicin 40 mg/m², vinblastine 9 mg/m², methotrexate 90 mg/m²</td>
<td>67</td>
<td>7.2</td>
<td>9.9</td>
</tr>
<tr>
<td>Pierga et al. [34]</td>
<td>20 (0)</td>
<td>Cisplatin 105 mg/m², doxorubicin 30 mg/m², etoposide 240 mg/m³, 5-FU 1800 mg/m³</td>
<td>45</td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>Lissoni et al. [35]</td>
<td>30 (0)</td>
<td>Cisplatin 50 mg/m², paclitaxel 175 mg/m³, epirubicin 70 mg/m²</td>
<td>73</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Dimopoulos et al. [36]</td>
<td>24 (0)</td>
<td>Cisplatin 75 mg/m², paclitaxel 175 mg/m³, etoposide 240 mg/m³, 5-FU 1800 mg/m³</td>
<td>67</td>
<td>8.4</td>
<td>17.6</td>
</tr>
<tr>
<td>Sorbe et al. [37]</td>
<td>44 (0)</td>
<td>Cisplatin 60 mg/m², vincristine 1.5 mg/m³, VM-26 100 mg/m³, megace 500 mg/day</td>
<td>52</td>
<td>NR</td>
<td>7</td>
</tr>
<tr>
<td>Gebbia et al. [38]</td>
<td>35 (0)</td>
<td>Cisplatin 80 mg/m², vinorelbine 50 mg/m²</td>
<td>57</td>
<td>NR</td>
<td>7.9</td>
</tr>
<tr>
<td>Pierga et al. [39]</td>
<td>49 (2)</td>
<td>5-FU 1800 mg/m³</td>
<td>41</td>
<td>NR</td>
<td>14</td>
</tr>
</tbody>
</table>

5-FU, 5-fluorouracil; NR, not recorded; OS, overall survival; PFS, progression-free survival.
trials, serious nausea and vomiting was increased almost threefold with the more intense regimens (OR = 2.73, 95% CI 1.76–4.23; \(P < 0.00001\)). Although there were few grade 3 or 4 diarrhoea/other GI events overall (29), there still seemed to be an excess with more compared with less chemotherapy (OR = 2.48, 95% CI 1.19–5.17; \(P = 5.1\%\)). Results for serious leucopenia were much more variable from trial to trial (\(I^2 = 89.5\%\)), with no statistically significant increase with more intense chemotherapy (OR = 1.30, 95% CI 1.19–5.17; \(P = 0.07\)). Grade 3 or 4 thrombocytopenia was increased more than four-fold with more chemotherapy (OR = 4.44, 95% CI 2.67–7.38; \(P < 0.00001\)) and this result was consistent across trials (\(I^2 = 19.2\%\)). Serious neurological toxicity was very rare, except in the trial of doxorubicin, cisplatin and paclitaxel versus doxorubicin and cisplatin [15], where it was significantly increased in the arm including paclitaxel (\(P = 0.0004\)).

Grade 3–4 alopecia, anaemia, cardiotoxicity, fever/infection, stomatitis/mucositis and renal/genitourinary toxicity were reported for fewer trials and also tended to be less frequent. Thus, the results of the formal analyses of these types of toxicity are less reliable. The overall tendency for these types of toxicity, however, was to be more frequent when more chemotherapy was given.

There were seven possible treatment-related deaths (1.8%) in one trial [11], but it is not clear whether these relate to one or other treatment. In another trial [15], five treatment-related deaths were attributable to the doxorubicin, cisplatin and paclitaxel arm but there were none on the doxorubicin and cisplatin arm. Aapro et al. [8] found that 10% of patients stopped treatment in the doxorubicin and cisplatin arm compared with 2% of patients receiving cisplatin alone.

other RCTs of chemotherapy

The other five trials addressed different chemotherapy questions and could not be combined for meta-analysis [6, 8, 12–14] (Table 1). There were no clear differences in response rates in all but two of these trials [6, 8]. There were no significant differences in PFS or OS for any of these trials (Table 1). The acute toxic effects reported were mainly haematological and GI, but tended to be similar irrespective of treatment regimen. Gallion et al. [10], however, found that grade 3 or 4 WBC toxicity (as per GOG scale) was significantly greater with standard-timed doxorubicin and cisplatin (75%) compared with circadian-timed doxorubicin and cisplatin (65%, \(P = 0.04\)). Other toxic effects did not appear to vary by treatment allocation.

phase II trials of chemotherapy

Eighty phase II non-randomised trials of the use of cytotoxic chemotherapy in advanced or recurrent endometrial carcinoma...
were identified, and 12 studies [17, 18] containing <15 patients were excluded. All studies included response rates, and 34 reported PFS, OS or both. Studies were divided up according to five broad categories of chemotherapy: cisplatin-containing regimens, carboplatin-containing regimens, paclitaxel-containing regimens (without platinum), anthracycline-containing regimens (without platinum) and miscellaneous single agents.

cisplatin-containing regimens. The 23 studies addressing the use of cisplatin alone or in combination are described in Table 2.

Three studies (113 patients) assessed the response to single-agent cisplatin [19–21]. One only included chemotherapy-naive patients [21]. Response was evaluated clinically or radiologically and varied from 4% to 42.3%. The lowest response rate was observed in women who had received previous chemotherapy [20]. Only one study reported survival, with a median of 8.2 months [21]. In all three studies, nausea and vomiting were the major toxic effects, but nephrotoxicity, neurotoxicity and mild myelosuppression were also common.

Four studies (involving 87 patients) assessed the response to combined cisplatin and doxorubicin [22–25] (Table 2). Two studies treated only chemotherapy-naive patients [22, 24], in one study it was not stated [23] and one study allowed prior chemotherapy [25]. Where stated, response was evaluated clinically or radiologically, and ranged from 36.8% to 81.2% (Table 2).

Six phase II trials of the CAP regimen were identified, involving 212 patients [26–30]. In two of these, megestrol acetate was also given [26, 31]. Response rates varied from 12.2% to 60%; in four studies, the response rate was >40%. Five studies (involving 184 patients) assessed response to cisplatin and doxorubicin in combination with other cytotoxic drugs [32–36] (Table 2). Prior progestogen use was permitted in all studies, but prior chemotherapy in only one [33]. Three studies assessed response radiologically [33, 34, 36]; while in the other studies, the method of assessment was not reported. Response rates varied from 30.9% to 75%, but no one regimen was consistently better than another (Table 2). Median survival ranged from 6.5 months [32] to 17 months [36]. Common toxic effects included myelosuppression and nausea and vomiting, with peripheral neuropathy, cardiotoxicity and stomatitis, also being reported.

Two studies (involving 54 patients) addressed the response to cisplatin in combination with a taxane in chemotherapy-naive patients [37, 38]. One [38] recruited patients who had progressed on progestogens or rapidly advancing disease not amenable to hormonal therapy. Both used the WHO criteria for assessing response and toxicity. The response rates were 73% [37] and 67% [38]. Median OS was 17.6 months in one study [38] and not stated for the other. In both studies, myelosuppression was a common toxic effect, as was mild neuropathy, and haematological toxicity was very frequent without the routine use of granulocyte colony-stimulating factor. In one study [38], 14 of 24 patients had improvements in their performance status and six in their pain score.
Three studies involving 128 patients investigated the use of cisplatin in combination with other cytotoxics. One study [39] gave cisplatin in combination with vincristine, megestrol acetate and the podophyllotoxin VM-26 (teniposide), another study [40] gave cisplatin in combination with vinorelbine and in the third study [41] cisplatin was combined with etoposide and 5-fluorouracil (5-FU).

carboplatin-containing regimens. Five studies addressed the use of carboplatin (Table 3); three of these used carboplatin as a single agent [42–44] and two used carboplatin in combination with one or more drugs [45, 46]. In total, 180 patients were enrolled in phase II trials of carboplatin-based chemotherapy and none. These patients had received prior chemotherapy. In all studies, response to treatment was assessed radiologically. Single-agent carboplatin resulted in overall response rates varying from 28% [43] to 33% [44], and median survival ranged from 7.1 months [43] to 10 months [44]. Toxicity was mainly grade 1 and 2 haematological.

Carboplatin in combination with methotrexate, 5-FU and megestrol acetate resulted in an ORR of 74% and a median survival of 16 months with only mild haematological and GI toxicity [45], and carboplatin in combination with paclitaxel resulted in an ORR of 60.9% [46].

anthracycline-containing regimens. Five studies involving 183 patients addressed the use of anthracyclines (Table 4), either alone or in combination with non-platinum drugs [47–51]. In two of these studies, prior chemotherapy was permitted [47, 50], while in the other three studies prior treatments were not reported. In two studies, it was not clear how assessment of response was made [47, 48]; in the other three studies, assessment was radiological.

Single-agent doxorubicin resulted in an ORR of 37.2% and a median survival of 6.8 months [47]. Toxicity was mainly haematological, but cardiac toxicity and nausea and vomiting were also reported. Pegylated doxorubicin resulted in an ORR of 9.5% and a median survival of 8.2 months in heavily pre-treated patients [50]. Toxicity was mainly haematological and was mild. Single-agent epirubicin resulted in an ORR of 25.9%, with median survival of 9.5 months [51]. The most frequent side-effect was nausea and vomiting and cardiac toxicity was not

Figure 3. Meta-analysis of Grade 3 and 4 toxicity combined (761 patients) for more intensive regimens compared to less intensive combination chemotherapy regimens for five of the six trials in advanced endometrial carcinoma analysed in Figures 1 and 2.
seen. Doxorubicin in combination with cyclophosphamide (oral or i.v.) resulted in an ORR of 30.7%; median survival was not reported [48]. Nausea and vomiting was the most frequently reported toxicity and admission to hospital for febrile neutropenia was required in five of 26 patients. Doxorubicin in combination with cyclophosphamide, 5-FU and megestrol acetate resulted in an ORR of 44.9% [49]. Median survival was not reported for the whole group.

**taxane-containing regimens.** Four studies involving 89 patients addressed the use of paclitaxel (Table 5), either alone or in combination with a non-platinum-based drug [52–55]. One of these studies only recruited patients with uterine papillary serous carcinoma, including both advanced disease and adjuvant therapy [54]. Another recruited patients with both advanced endometrial carcinoma and uterine sarcoma [55]. Radiological imaging was carried out regularly in two studies [53, 54]. In three studies, no prior chemotherapy was allowed [52, 54, 55] while in the fourth study, prior chemotherapy with cisplatin, cyclophosphamide and doxorubicin was one of the criteria for eligibility [53]. Single-agent paclitaxel achieved response rates of 35.7% [52] to 77% [54]. The response rate to paclitaxel in patients previously treated with chemotherapy was 37%, and 47% of these patients were considered to have platinum-resistant disease [53]. Median survival was only reported in one study at 9.5 months [52]. Myelosuppression was common, although it was milder in the study using lower dose paclitaxel [53]. Arthralgia, myalgia and neuropathy were also reported. Paclitaxel in combination with liposomal doxorubicin resulted in an ORR of 40.7% but survival was not reported [55]. The most frequently reported toxic effects were myelosuppression and plantar–palmar erythema.

**miscellaneous single agents and combinations.** A further 28 phase II trials involving 789 patients of single agents not included in the above categories were identified and there is one further study of melphalan, 5-FU and a progestogen containing 11 assessable patients (data not shown).

**Table 3. Characteristics of phase II trials of chemotherapy: carboplatin-containing regimens**

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Patients recruited (and having prior chemotherapy)</th>
<th>Chemotherapy</th>
<th>Overall response rate (%)</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long et al. [41]</td>
<td>25 (0)</td>
<td>Carboplatin 400 mg/m^2</td>
<td>28</td>
<td>3.8</td>
<td>7.1</td>
</tr>
<tr>
<td>Green et al. [40]</td>
<td>32 (0)</td>
<td>Carboplatin 400 mg/m^2</td>
<td>30</td>
<td>NR</td>
<td>9.3</td>
</tr>
<tr>
<td>Burke et al. [42]</td>
<td>33 (0)</td>
<td>Carboplatin 360–450 mg/m^2</td>
<td>33</td>
<td>4–5</td>
<td>8–10</td>
</tr>
<tr>
<td>Bafaloukos et al. [43]</td>
<td>23 (0)</td>
<td>Carboplatin 300 mg/m^2, methotrexate 30 mg/m^2, 5-FU 500 mg/m^2, megace 300 mg/day</td>
<td>74</td>
<td>NR</td>
<td>16</td>
</tr>
<tr>
<td>Hoskins et al. [44]</td>
<td>67 (0)</td>
<td>Carboplatin AUC 5–7, paclitaxel 175 mg/m^2</td>
<td>61</td>
<td>NR</td>
<td>15–26</td>
</tr>
</tbody>
</table>

AUC, area under the curve; 5-FU, 5-fluorouracil; NR, not recorded; OS, overall survival; PFS, progression-free survival.

**Table 4. Characteristics of phase II trials of chemotherapy: anthracycline-containing regimens**

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Patients recruited (and having prior chemotherapy)</th>
<th>Chemotherapy</th>
<th>Overall response rate (%)</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thigpen et al. [45]</td>
<td>55 (2)</td>
<td>Doxorubicin 60 mg/m^2</td>
<td>37</td>
<td>NR</td>
<td>6.8</td>
</tr>
<tr>
<td>Seski et al. [46]</td>
<td>26 (NR)</td>
<td>Doxorubicin 40–50 mg/m^2, cyclophosphamide 500–600 mg/m^2</td>
<td>30</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Deppe et al. [47]</td>
<td>29 (NR)</td>
<td>Doxorubicin 40 mg/m^2, cyclophosphamide 400 mg/m^2, 5-FU 400 mg/m^2, megace 160 mg/day</td>
<td>45</td>
<td>NR</td>
<td>6.7–12.5</td>
</tr>
<tr>
<td>Muggia et al. [48]</td>
<td>46 (40)</td>
<td>Pegylated liposomal, doxorubicin 50 mg/m^2</td>
<td>9</td>
<td>NR</td>
<td>8.2</td>
</tr>
<tr>
<td>Calero et al. [49]</td>
<td>27 (0)</td>
<td>Epirubicin 80 mg/m^2</td>
<td>26</td>
<td>6</td>
<td>9.5</td>
</tr>
</tbody>
</table>

5-FU, 5-fluorouracil; NR, not recorded; OS, overall survival; PFS, progression-free survival.

**discussion**

Phase II data show that a number of drugs have some activity in advanced endometrial cancer. The most commonly investigated drugs include platinums, anthracyclines and taxanes, either alone or in combination. The patients, however, were selected according to different criteria and some were variously pre-treated. Therefore, in the absence of a randomised control group, it is not possible to tell whether any of the combinations are superior in terms of PFS, OS, palliation of symptoms or effects on QoL.

In total, 778 women participated in phase II trials of cisplatin-based chemotherapy with response rates ranging from 4% to 81.2%. Median survival was not reported for all studies but varied from 6.5 months [32] to 17.6 months [38], and higher response rates did not always correlate with longer survival. The combination of cisplatin with paclitaxel resulted in an
impressive response rate and the longest median survival in a small group of heavily pre-treated patients [38]. A total of 180 patients were enrolled in phase II studies of carboplatin-based chemotherapy. The response rates and median OS from these studies do not indicate that carboplatin is inferior to cisplatin in the therapy of advanced endometrial cancer. Myelosuppression may be more frequent but nephrotoxicity, neurotoxicity and emesis were all less frequently reported and were milder than those in cisplatin-based regimens. Carboplatin in combination with paclitaxel appears as active as cisplatin in combination with paclitaxel [46].

A total of 183 patients were enrolled in phase II studies of anthracyclines, either alone or in combination with non-platinum drugs. Response rates varied from 9.5% (60) with pegylated doxorubicin in heavily pre-treated patients to 44.9% (49). The response rates for doxorubicin in combination with non-platinum drugs were similar to the response rates achieved by single-agent, non-pegylated doxorubicin. The response rates for single-agent anthracyclines compare quite favourably with those for single-agent platinum.

A total of 89 patients were enrolled in phase II studies of paclitaxel, either alone or in combination with a non-platinum drug. Single-agent response rates appear similar to anthracyclines and platinum drugs used alone. The response rates reported in one small trial [53] seem impressive given that all patients in this study had received prior chemotherapy and just under half had disease described as platinum resistant.

The quality of the 11 identified RCTs of cytotoxic chemotherapy in advanced or recurrent endometrial adenocarcinoma randomly assigning 2288 women was somewhat variable. Response rates varied between RCTs, with the worst rates in the most heavily pre-treated patients [8, 9]. In a number of trials, combination therapy led to a higher response than single-agent treatment or other combinations [7, 10, 11], but with the exception of Fleming et al. [13], this better response rate did not translate into better PFS or OS, at least at the individual trial level. A meta-analysis of the six trials that compared more intense chemotherapy combinations indicates that more intense chemotherapy significantly improves the median PFS, but not OS. This is, however, at the expense of increased grade 3/4 toxicity. It should be noted that a number of these trials pre-date the routine use of the type 3 serotonin receptor (5-HT3) antagonists and the rate of grade 3 and 4 vomiting may be higher than what one would expect in current practice. Across these six trials, the results are fairly consistent and no one regimen appears superior to another in improving PFS and OS. The only RCT that reported a significant improvement in PFS and OS was that of doxorubicin, cisplatin and paclitaxel versus doxorubicin and cisplatin [15] with the benefit associated with the paclitaxel-containing arm. Grade 3 or 4 thrombocytopenia and neurological toxicity, however, were also significantly greater and there were five treatment-related deaths with the paclitaxel arm.

There was no clear evidence from the RCTs comparing other miscellaneous chemotherapy regimens or schedules that any were superior in terms of OS and PFS and/or reduced toxicity. The median survival varied from 7 to 15 months and median PFS varied from 2.5 to 8 months. These may reflect prior treatments and stage of disease, as well as the effect of any particular regimen. One additional trial compared doxorubicin and cisplatin chemotherapy with whole-abdominal radiotherapy (WAR), and showed a survival gain for the cytotoxic chemotherapy arm [54]. While it did not meet the inclusion criteria for this review, if the assumption is made that WAR does not adversely affect survival, then this is indirect evidence that combination chemotherapy improves survival in endometrial cancer.

Conclusions on the potential of chemotherapy to palliate symptoms and improve QoL are limited given the modest potential impact of chemotherapy on PFS and OS, and collection of such patient-reported data should be a priority in future research. Response rates up to 75% were, however, reported and response may be regarded as a crude surrogate for palliation if maintained for several months.

Clinicians may consider chemotherapy for patients with more aggressive disease or visceral disease, or may offer it to younger patients of good performance status. The RCTs enrolled a heterogeneous group of patients in terms of prior therapies and hormonal agents or cytotoxic agents. The phase II data show a lack of cross-resistance between cisplatin and paclitaxel and that response rates for doxorubicin/cisplatin combinations are much higher than those for single agents. Performance status was not reported in all studies, yet may have a significant impact on how much benefit a patient obtains from treatment. The data indicate that the increased toxicity associated with the use of more than two drugs is not justified by the slight improvement in outcome. There is no data regarding correlation between sites of metastatic disease and benefit. The effect of co-morbidity is also difficult to establish and may vary with ethnic background and socioecomonic group.
conclusions

There is a need for a trial that randomly assigns women with advanced disease and no prior treatment with endocrine or cytotoxic therapy to receive chemotherapy or endocrine therapy. GOG 189 attempted this but failed to recruit. European Organisation for Research and Treatment of Cancer (EORTC 55984) randomly assigned patients between cisplatin and doxorubicin with or without paclitaxel and also had difficulty in recruitment for reasons which included concerns over the toxicity of both arms [55]. Clinicians therefore have to consider whether the modest survival gain of the order of 3 months justifies the toxicity of a three-drug combination in the individual patient. Assessment of baseline and on-treatment QoL and symptom scores should supplement primary outcomes such as PFS and OS. The optimum chemotherapy regimen to be used is not established, but there is wide experience in other tumours with the use of carboplatin and paclitaxel together, and this combination merits consideration in endometrial cancer as well as cisplatin and liposomal doxorubicin for which more limited data exist [56]. Future trials may also clarify which groups of patients would benefit from which treatment by stratifying patients at trial entry for tumour grade, prior therapies, performance status, site of disease and co-morbidity. Molecular parameters such as hormone receptor status, topoisomerase I/II and possibly growth factor pathway activation status need to be evaluated for their prognostic value and ability to predict sensitivity to the anthracyclines, platinum drugs and taxanes. These factors are likely to be even more important in evaluating novel agents such as the mTOR inhibitors, which is in order to design adjuvant chemotherapy trials for high-risk stage I patients (such as the PORTEC 3 study); it is also vital that good quality data be acquired from the treatment of patients with advanced disease.

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references