Systemic therapy for advanced uterine sarcoma: a systematic review of the literature
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CRD summary
This review assessed systemic treatments for advanced uterine sarcoma. The authors concluded that offering palliative chemotherapy to these patients is reasonable, that the response rate to treatment appears to vary with histological type, and that further research is required. There were limitations to the review, but the authors' cautious conclusions appear to reflect the limited evidence.

Authors' objectives
To assess systemic treatments for advanced, recurrent or metastatic uterine sarcoma.

Searching
MEDLINE (1980 to June 2004), EMBASE (1980 to week 25, 2004), Cancerlit (1980 to October 2002) and the Cochrane Library (Issue 1, 2004) were searched using the reported search terms. Conference proceedings of the American Society of Clinical Oncologists (1997 to 2004) and reference lists in retrieved studies and relevant reviews were screened. In addition, the websites of CMA Infobase and the National Guideline Clearinghouse were searched for existing evidence-based guidelines.

Study selection
Study designs of evaluations included in the review
Systematic reviews, practice guidelines, meta-analyses and randomised controlled trials (RCTs) were eligible for inclusion. Prospective phase II trials or retrospective reviews that involved at least 20 patients were also eligible.

Specific interventions included in the review
Studies of systemic treatments were eligible for inclusion. The included studies used various single-agent and combination chemotherapy regimens as first- and second-line treatment. The most commonly used agents were doxorubicin, cisplatin and ifosfamide (full details of the regimens were reported). The comparator interventions were not specified but included best supportive care, an alternative single-agent chemotherapy, or combination therapy.

Participants included in the review
Studies of patients with advanced, recurrent or metastatic uterine sarcoma were eligible for inclusion. The review focused on three subtypes of uterine sarcoma: mixed mesodermal tumours (MMTs), leiomyosarcoma (LMS) and endometrial stromal sarcoma.

Outcomes assessed in the review
Studies were eligible if they assessed response rate (RR), time to progression, overall survival or toxicity.

How were decisions on the relevance of primary studies made?
Three reviewers selected studies, but it was unclear whether the selections were made independently.

Assessment of study quality
It was not clear whether any formal assessment of validity was conducted, although elements of methodological quality were noted in the individual descriptions of the RCTs.

Data extraction
The authors did not clearly state how the data were extracted for the review, or how many reviewers performed the data extraction. For each treatment arm, where possible, the number of patients with each outcome of interest and the
median time to the event of interest were extracted.

Methods of synthesis
How were the studies combined?
The RCTs were described individually. The phase II trials were grouped by histology and type of treatment (first- or second-line) then combined in a narrative with accompanying tables. For phase II trials, pooled weighted mean RRs with 95% confidence interval (CIs) were calculated for single-agent and combination therapy for different histological subtypes, and for first- and second-line treatments.

How were differences between studies investigated?
Differences between the studies were discussed in the text; additional differences were evident from the tables.

Results of the review
Three RCTs (n=524) and 24 non-comparative prospective phase II studies (n=768) were included in the review.

RCTs (3 studies).

One non-blinded RCT (n=194) compared ifosfamide plus mesna uro-protection versus ifosfamide plus mesna plus cisplatin as first-line treatment of chemotherapy-naive women with MMT. It found that the objective RR was significantly greater with ifosfamide plus cisplatin than with ifosfamide alone (54% versus 36%, P=0.03). Combination treatment also significantly increased progression-free survival (median 6.0 versus 4.0 months, P=0.02), but there was no significant difference between treatments for overall survival (median 7.6 versus 9.4 months, P=0.07). Combination treatment was associated with more deaths (6 versus none), increased granulocytopenia (60% versus 36%), anaemia (17% versus 8%), peripheral neurological symptoms (12% versus 1%) and cardiac symptoms (3% versus 0%). Central neurological symptoms were more common with the single-agent regimen (19% versus 14%). The treatment groups were not comparable at baseline and the number of full treatments also differed.

One non-blinded RCT (n=104) compared doxorubicin plus cyclophosphamide versus doxorubicin alone as first-line treatment in chemotherapy-naive women with all histological subtypes of uterine sarcoma. It found the same RR with both treatments in patients with measurable disease (19%). There was no significant difference between treatments for progression-free survival (median 5.1 versus 4.9 months, P=0.22) or overall survival (median 11.6 versus 10.9 months, P=0.55). Combination treatment significantly increased grade 3 and 4 leukocyte toxicity (35% versus 10%).

The third non-blinded RCT (n=226) compared doxorubicin plus DTIC (dimethyl triazenoimidazole carboxamide) versus doxorubicin alone as first or second-line treatment in chemotherapy-naive women with all histological subtypes of uterine sarcoma (mainly LMS and MMT). It found a significantly higher RR with the combination treatment (P<0.05), with higher RRs seen for both MMT (23% versus 10%) and LMS (30% versus 25%). There was no significant difference between treatments for progression-free survival (3.5 versus 5.5 months) or overall survival (7.7 versus 7.3 months). Combination treatment significantly increased grade 3 and 4 haematological (48% versus 20%) and gastrointestinal toxicity (9% versus 2%) compared with the single-agent treatment.

Non-comparative phase II studies (24 studies).

For first-line treatment of patients with LMS, the pooled RR was higher with combination treatment than with single-agent regimens (22.7% versus 7.1%). For patients with MMT, the pooled RR was higher with single agents (22.1% versus 15.7%).

For second-line treatment of patients with LMS, the pooled RR was higher with combination treatment than with single-agent regimens (53.0% versus 7.0%). For patients with MMT, the pooled RR for single-agent regimens was 6.7% (there were no studies of combination chemotherapy in MMT).

The fewest adverse effects were found for first-line treatment with aminothiadiazole, cisplatinum, etoposide and paclitaxel. More adverse effects were found with second-line treatments compared with first-line treatments.
Authors' conclusions
It is reasonable to offer palliative chemotherapy to women with symptoms from advanced unresectable uterine sarcoma. The response to treatment appeared to vary with histological type. There was insufficient evidence to assess the effect of treatment on overall survival and quality of life. Further research is required.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design; inclusion criteria for study design were broad, but this appeared appropriate. Several relevant sources were searched and attempts were made to minimise publication bias. It was not clear whether any language limitations had been applied, so the potential for language bias could not be assessed. The methods used to select studies and extract the data were not reported in full, thus it was unclear what efforts were made to reduce reviewer errors and bias. The studies were appropriately grouped by study design and some methodological limitations of the RCTs were discussed. However, it was not clear whether a systematic validity assessment of the RCTs had been conducted; there was no mention of whether analyses were conducted on an intention-to-treat basis. Some of the limitations of evidence from the uncontrolled phase II trials were discussed, and the authors correctly highlighted the limited conclusions that could be drawn from indirect comparisons of RRs using data from the phase II trials. The review had its limitations, but the authors' cautious conclusions appear to reflect the limited evidence.

Implications of the review for practice and research
Practice: The authors stated that it is reasonable to offer palliative chemotherapy to patients with symptoms from advanced unresectable uterine sarcoma. They stated that options include single-agent doxorubicin in a dose of at least 60 mg/m² every 3 weeks (support from 2 RCTs of first-line treatment) and ifosfamide alone or in combination with cisplatinum in women with advanced MMTs, but that combination treatment increases adverse effects.

Research: The authors stated that future trials should examine the effects of treatments on different histological subtypes of malignant uterine sarcoma using stratification or by targeting only patients with specific histologies. They also stated there is a need for further research to assess if the high RR found for gemcitabine plus docetaxel for second-line treatment of LMS translates into differences in progression-free survival or overall survival.

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