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Systemic Therapy for Advanced, Recurrent, or Metastatic Uterine Sarcoma Evidence Summary Report #4-12

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An evidence summary report is a systematic overview of the best evidence available on a specific clinical question when there is insufficient high-quality evidence on which to base practice recommendations.

SUMMARY

Questions

1. Does systemic therapy (including hormonal treatment, single agent chemotherapy, or combination chemotherapy) improve outcomes (e.g., response rate, time to progression, overall survival, and toxicity) in women with advanced, recurrent, or metastatic unresectable uterine sarcoma?
2. In this population, are particular systemic therapies preferable for particular histological subtypes?
3. Are there significant differences in toxicities between the chemotherapy regimens?

Target Population

This evidence summary applies to women with newly diagnosed advanced, recurrent, or metastatic unresectable uterine sarcomas who are eligible for systemic chemotherapy. The indications for treatment with systemic chemotherapy include relief of symptoms secondary to advanced uterine sarcoma and prolongation of survival.

Opinions of the Gynecology Cancer Disease Site Group

The lack of sufficient high quality evidence precludes definitive recommendations at this time. Instead, the Gynecology Cancer Disease Site Group offers the following opinions based on the evidence reviewed:

- It is reasonable to offer palliative chemotherapy to patients with advanced, unresectable uterine sarcoma who are symptomatic from this disease. This opinion is based on Phase II and III trials that report partial and complete responses and improvements in median survival time with systemic chemotherapy. There are no trials that compare systemic therapy to best supportive care in women with advanced uterine sarcoma, nor are there quality of life data available to assess the impact of chemotherapy on these patients.

- Single agent doxorubicin, given in a dose of at least 60mg/m² every three weeks, is a reasonable option for palliation of women with advanced or metastatic uterine sarcoma, who are eligible for chemotherapy. This opinion is based on the results of two small randomized controlled trials (N=86, N=226) of first-line treatment.
- The combination of cisplatin and ifosfamide is also a reasonable option for women with advanced or metastatic mixed mesodermal tumours; however, this combination is associated with significant toxicity when compared to ifosfamide alone. Therefore, patients should be selected carefully based on age, performance status, and comorbidities.
- Gemcitabine combined with docetaxel has shown promising phase II study results for patients undergoing second-line therapy for leiomyosarcoma. Further research is required to assess if the high response rates are associated with an important difference in progression-free survival or overall survival. In the absence of randomized trials, this phase II data provides reasonable evidence that this combination of chemotherapy is a rational option for the second-line treatment of patients with progressive, symptomatic metastatic leiomyosarcoma.
- There is insufficient evidence to comment on treatments specifically for endometrial stromal sarcoma.
- There are not enough high-quality randomized controlled trials examining the role of systemic therapy in relation to overall survival and quality of life in patients with advanced, recurrent, or metastatic uterine sarcoma. Such trials would be of benefit to the gynecologic oncology community and the patients they serve. Patients and practitioners should be encouraged to take part in such trials.

Key Evidence

- Three randomized controlled trials and 22 prospective phase II trials were identified that described systemic treatment for advanced, recurrent, or metastatic uterine sarcoma.
- In a randomized controlled trial of first-line treatment with doxorubicin versus doxorubicin plus cyclophosphamide for advanced or recurrent uterine sarcoma (all histologic subtypes), single agent doxorubicin at a dose of 60 mg/m² every three weeks produced an overall response rate of 19% and median survival of 11.6 months, which was no different from the result with combination chemotherapy (response rate 19%, median survival 10.9 months).
- A randomized controlled trial comparing the combination of ifosfamide plus cisplatin versus ifosfamide alone in mixed mesodermal tumours (first- and second-line treatment) showed a significant improvement in response rate and progression-free survival with the two-drug combination compared with the single agent alone. The combination was also associated with more toxicity.
- The randomized trial that compared doxorubicin (60mg/m² every three weeks) alone to doxorubicin with diethyl triazenoimidazole carboxamide (DTIC 250mg/m² every three weeks) in women with advanced or recurrent uterine sarcoma demonstrated a significantly higher response rate with the combination (p<0.05). However, there was no significant difference in survival.
- Only one small study was identified that specifically evaluated treatment in patients with endometrial stromal sarcoma histology. First-line treatment with single agent ifosfamide (1.5g/m² daily for 5 days every three weeks) produced a response rate of 33% in a prospective phase II study.
- There was one small prospective phase II study that examined the use of gemcitabine and docetaxel in women with uterine sarcoma. The study reported the outcomes of second-line therapy in women with leiomyosarcoma treated with the combination of gemcitabine

(900mg/m² day 1 and 8) and docetaxel (100mg/m² day 8) every three weeks. The study reported a response rate of 53% and median survival of 17.1 weeks.

Methods

Entries to MEDLINE (1980 through June 2004), EMBASE (1980 through week 25, 2004), CANCERLIT (1980 through October 2002), and Cochrane Library (2004, Issue 1) databases and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology (1997 to 2004) were systematically searched for evidence relevant to this evidence summary report.

Evidence was selected and reviewed by three members of the Practice Guidelines Initiative's Gynecology Cancer Disease Site Group and methodologists. This evidence summary report has been reviewed and approved by the Gynecology Cancer Disease Site Group, which comprises gynecologic oncologists, medical oncologists, radiation oncologists, an oncology nurse, a pathologist, patient representatives, and methodologists.

External review by Ontario practitioners is obtained for all evidence summary reports through a mailed survey. Final approval of the evidence summary report is obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each evidence summary report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original evidence summary.

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*The Practice Guidelines Initiative is sponsored by:
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PREAMBLE: About Our Evidence Summary Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care (PEBC). The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.¹

An evidence summary report is a systematic overview of the best evidence available on a specific clinical question when there is insufficient high-quality evidence on which to base a practice guideline. The report is intended as information for individuals and groups to use in making decisions and policies where the evidence is uncertain. For example, the evidence comes from uncontrolled studies, from studies with control groups that are not relevant to current practice in Ontario, or from subgroup analyses, or the evidence consists solely of preliminary results from ongoing trials. The PEBC will monitor the scientific literature and will develop a practice guideline on this topic when more evidence becomes available.

This evidence summary report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, patient representatives, and CCO executives. Formal approval of an evidence summary by the Coordinating Committee does not necessarily mean that the evidence summary has been adopted as a practice policy of CCO. The decision to adopt an evidence summary as a practice policy rests with each regional cancer network, which is expected to consult with relevant stakeholders, including CCO.

Reference:

¹ Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

For the most current versions of the evidence summary reports and information about the PGI and the Program, please visit the CCO Internet site at:

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FULL REPORT

I. QUESTIONS

1. Does systemic therapy (including hormonal treatment, single agent chemotherapy, or combination chemotherapy) improve outcomes (e.g. response rate, time to progression, overall survival, and toxicity) in women with advanced, recurrent, or metastatic, unresectable uterine sarcomas?
2. In this population, are particular systemic therapies preferable for particular histological subtypes?
3. Are there differences in toxicities between the chemotherapy regimens?

II. CHOICE OF TOPIC AND RATIONALE

Uterine sarcomas are a rare group of neoplasms with a worldwide annual incidence of between 0.5 and 3.3 cases per 100,000 women. The annual incidence of uterine sarcoma in a large cancer registry in the United Kingdom was 1/100,000 women; 87% (367/423) of these were mixed mesodermal tumours or leiomyosarcoma (LMS) (1). Uterine sarcomas account for less than four percent of all malignancies of the uterine corpus. They are a heterogeneous group of tumours with many pathologic subtypes that present with a varying natural history from a benign course to aggressive disease (2).

According to an analysis of the Surveillance, Epidemiology, and End Results (SEER) Program data, mixed mesodermal tumours (carcinosarcoma) were the most common uterine sarcoma (0.82/100,000), followed by LMS (0.64/100,000) and endometrial stromal sarcoma (0.19/100,000). There are a number of other pathological subtypes, but these are so rare that they account for a very small proportion of cases (0.05/100,000) and are not usually identified separately in clinical trials (3).

Uterine sarcomas can be classified as pure sarcomas, containing only a mesenchymal component, or mixed, containing a mesenchymal and epithelial component. Pure sarcomas can be either homologous, meaning that the mesenchymal tissue differentiates into tissue that is normally found in the uterus, or heterologous, meaning that the mesenchymal tissue may differentiate into tissue not normally found in the uterus. Pure homologous sarcomas include LMS and endometrial stromal sarcomas. These can be either indolent, low-grade tumours or the more common aggressive high-grade tumours. Pure heterologous sarcomas are extremely rare (4).

Mixed sarcomas consist of tumours, which contain an epithelial and mesenchymal component. These include indolent tumours with a benign epithelial component and malignant mesenchymal component such as adenosarcoma, and aggressive tumours in which both the epithelial and mesenchymal components are malignant, known as carcinosarcoma. This group of aggressive tumours is also called malignant mixed mullerian tumour or mixed mesodermal tumours (MMT) and will be referred to as such in this paper. MMTs are highly aggressive, usually arise in elderly post-menopausal women, and often present with an advanced stage. The overall prognosis is usually poor (2).

In recent years, the pathological classification of MMT has been challenged. Evidence has emerged that many MMTs are actually monoclonal, as they are derived from a single stem cell. The carcinomatous element appears to be the central force while the sarcomatous element is a result of dedifferentiation (5). Therefore, these tumours may be better described as carcinomas with sarcomatous metaplasia, rather than true mixed tumours. This pathological distinction has important clinical implications since it has been suggested that these tumours should be treated as endometrial adenocarcinomas rather than as sarcomas (6).

Low-grade sarcomas often have an indolent natural history, and long-term survival has been reported after surgical resection. Disease usually recurs locally with a long disease-free interval (5).

MMT, high-grade LMS, and endometrial stromal sarcoma behave in an aggressive fashion. The interval from the onset of symptoms to diagnosis of early stage disease ranges from two to five months. Patients who present with early stage disease confined to the uterus have a two to five year overall survival of approximately 50% (7). In a prospective, multi-centre surgical staging trial from the GOG (Gynecologic Oncology Group), 71% of the patients with LMS and 53% of the patients with MMT recurred (8).

Autopsy studies have shown a high incidence of nodal and lung metastases in women with metastatic uterine sarcoma (9). Pulmonary metastases are more common in LMS and extra-pulmonary recurrences are more common in MMT (10). Selected patients with lung metastases should be considered for thoracotomy and resection of lung metastases. In a retrospective review of patients with pulmonary metastasis from various primary tumours; those who underwent pulmonary metastasectomy for advanced soft-tissue sarcoma were reported to have five-year survival rates post-resection of 33% (11). Another retrospective review, this time specifically looking at patients with isolated pulmonary metastases from uterine sarcoma, reported actuarial five- and ten-year survival rates (from time of resection of pulmonary metastases) of 43% and 35% respectively. The median follow-up was 25 months. Unilateral versus bilateral pulmonary disease was a significant predictor of survival after pulmonary resection. Therefore, in this selected population who underwent pulmonary metastasectomy for advanced uterine sarcoma, long-term survival was achieved by a substantial proportion of patients (12).

In general, the median survival for metastatic MMT is less than one year. There are a few cases of long-term survivors after resection of lung metastases (12). Patients with LMS that has spread beyond the uterus and is judged unresectable rarely attain long-term survival, unless the tumour is very low-grade (13). Typically management of metastatic uterine sarcoma conforms to treatment practice for metastatic soft tissue sarcomas. The principles of management include surgical resection of isolated metastases, radiation to sites of local recurrence for optimal disease control and palliative systemic chemotherapy for advanced disease.

The Gynecology Cancer Disease Site Group (Gynecology Cancer DSG) decided to develop an evidence summary in order to review the current available evidence for the systemic therapy treatment of advanced, recurrent, or metastatic uterine sarcoma. This evidence summary focused on the three subtypes of uterine sarcoma that account for more than 90% of advanced uterine sarcomas: mixed mesodermal tumours, leiomyosarcoma, and endometrial stromal sarcoma.

III. METHODS

Evidence Summary Development

This evidence summary report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario's Program in Evidence-based Care (PEBC), using the methods of the Practice Guidelines Development Cycle (14). Evidence was selected and reviewed by three members of the PGI's Gynecology Cancer DSG and methodologists. There were no conflicts of interest disclosed by the members of the Gynecology Cancer DSG.

The evidence summary report is a convenient and up-to-date source of the best available evidence on advanced, recurrent, or metastatic uterine sarcoma developed through systematic reviews, evidence synthesis, and input from practitioners in Ontario. In contrast to the practice guidelines, the body of evidence in an evidence summary is less mature and is comprised of data primarily from non-randomized controlled trial data or data available only in abstract form. This precludes the development of definitive recommendations and instead, opinions of the DSG are offered. The report is intended as information for individuals and groups to use in making decisions and policies where the evidence is uncertain. The Practice

Guidelines Initiative is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners is obtained for all evidence summary reports through a mailed survey consisting of items that address the quality of the evidence summary report, the interpretation of the available evidence, and whether there is a need to develop an evidence-based practice guideline when sufficient evidence is available. Final approval of the evidence summary report is obtained from the Practice Guidelines Coordinating Committee (PGCC).

The PGI has a formal standardized process to ensure the currency of each evidence summary report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original evidence summary.

Literature Search Strategy

MEDLINE (1980 to June 2004), EMBASE (1980 through week 25, 2004), CANCELIT (1980 to October 2002) and the Cochrane Library (2004, Issue 1) databases were searched. “Uterine sarcoma” (Medical subject heading (MeSH)), “leiomyosarcoma” (MeSH), and “mixed mesodermal tumour” (MeSH) were combined with the search terms for the following study designs and publication types: practice guidelines, systematic reviews or meta-analyses, reviews, randomized controlled trials, and controlled clinical trials. The full search strategy is listed in Appendix 1. In addition, the conference proceedings of the American Society of Clinical Oncologists (1997 to 2004) were searched for reports of new trials. Relevant articles and abstracts were selected and reviewed by three reviewers and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles. The Canadian Medical Association Infobase (<http://mdm.ca/cpgsnew/cpgs/index.asp>) and the National Guidelines Clearinghouse (<http://www.guideline.gov/index.asp>) were searched for existing evidence-based practice guidelines.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were:

1. Systematic reviews, practice guidelines, meta-analyses, or randomized controlled trials (RCT) comparing systemic therapy treatment regimens for advanced, recurrent, or metastatic uterine sarcoma or;
2. Prospective phase II trials or retrospective reviews reporting the effects of systemic therapy treatment for ≥ 20 patients with advanced, recurrent, or metastatic uterine sarcoma.
3. The studies included at least one outcome of interest: response rate, time to progression, overall survival, or toxicity.

Exclusion Criteria

This systematic review of the evidence did not consider:

1. Phase II studies with < 20 patients because smaller studies are more likely to overestimate benefits and provide low confidence limits.
2. Case studies.
3. Letters and editorials.
4. Papers published in a language other than English.

Synthesizing the Evidence

To obtain an overall estimate of response rates, the weighted mean for response rate was calculated using the following formula:

$$p_w = \text{sum}(w_i * v_i) / \text{sum}(w_i)$$

where,

$$w_i = 1/v_i$$

$$v_i = p_i * (1 - p_i) / n_i$$

p_i = proportion for study i

p_w = the weighted mean of the M studies

n_i = the total number of subjects in study i.

w_i = the weight for study i

v_i = the variance of the estimated proportion in study i

The weighted mean was calculated overall, according to recurrence (first or second), and according to histology where studies reported response rates by histology. The Gynecology Cancer DSG chose to pool the response rates across the studies because response data were consistently reported across the studies. The other outcomes of interest were reported less consistently and thus were not pooled.

IV. RESULTS

Literature Search Results

There were no existing practice guidelines, consensus statements, or systematic reviews identified that investigated systemic therapies for advanced, recurrent, or metastatic uterine sarcoma.

There were 25 studies that met the inclusion criteria for this evidence summary (Table 1). Three RCTs were identified (15-17) that compared single agent versus combination chemotherapy. In addition to the three RCTs, 22 prospective phase II studies (18-39) form the bulk of the evidence for this report.

The RCT by Sutton et al (15) compared single agent ifosfamide with combination ifosfamide and cisplatin in first-line treatment of advanced MMT. Omura et al (16) compared single agent doxorubicin with combination doxorubicin and dimethyl triazenoimidazole (DTIC) in second-line treatment of advanced uterine sarcoma. The third RCT reported by Muss et al (17) compared single agent doxorubicin with combination doxorubicin and cyclophosphamide in first-line treatment of advanced uterine sarcoma.

There were no comparisons of chemotherapy versus best supportive care, single agent chemotherapy versus single agent chemotherapy, or combination chemotherapy versus combination chemotherapy.

Table 1. Studies included in the evidence summary.

Histologic Subtype		Number of Randomized Controlled Trials (study reference)	Number of Prospective Phase II Trials (study reference)
Leiomyosarcoma	First-line therapy	1 (17) ^a	7 (18-23) (24) ^b
	Second-line therapy	1 (16) ^a	8 (25-32)
Mixed mesodermal sarcoma	First-line therapy	2 (17) ^a (15)	2 (24) ^b (33)
	Second-line therapy	1 (16) ^a	5 (34-38)
Endometrial stromal sarcoma	First-line therapy	No studies identified	1 (39)
	Second-line therapy		No studies identified

^a Did not report results for separate histologic subtypes

^b Reports separate results for leiomyosarcoma and mixed mesodermal sarcoma

Randomized Controlled Trials of Systemic Therapy

Two of the three RCTs identified for this evidence summary reported results for advanced uterine sarcoma but did not provide specific results according to histologic subtypes (16,17). The third RCT, by Sutton et al (15), limited its eligibility criteria to include only patients with MMT. Details of the RCTs are presented in Table 2.

The RCT by Sutton et al (15) was a non-blinded, multicentre, randomized trial for first-line treatment of advanced or recurrent MMT uterine sarcoma that compared ifosfamide with mesna uro-protection to ifosfamide with mesna plus cisplatin. Ifosfamide doses were decreased by 20% in patients who had received previous pelvic irradiation. The regimen was subsequently changed, while the trial was ongoing, from a five-day regimen to a four-day treatment period, due to excess early toxicity.

One hundred and ninety-four chemotherapy-naïve women participated in the trial. The treatment arms were unbalanced in terms of sites of measurable disease: 37% of patients in the ifosfamide alone arm and 59% in the combination arm had measurable disease limited to the pelvis. Fewer patients in the combination arm received all eight courses of therapy (70% versus 80%). Six patients in the combination arm suffered treatment-related deaths (four from granulocytopenic sepsis, one from hemorrhagic stroke with thrombocytopenia, and one due to severe nausea and vomiting leading to aspiration). All six had received the original full dose of chemotherapy during the early portion of the study before the official dose reduction. There were no treatment-related deaths reported in the ifosfamide-alone arm.

There was a significantly greater objective response rate among patients treated with the combination of ifosfamide and cisplatin compared with ifosfamide alone (54% versus 36%, respectively, $p=0.03$). There was also an improvement in progression-free survival for the combination of ifosfamide and cisplatin versus ifosfamide (median 6.0 versus 4.0 months, respectively, $p=0.02$). However, there was no significant difference in overall survival (median 7.6 versus 9.4 months, $p=0.07$).

The RCT by Muss et al (17) compared doxorubicin alone to doxorubicin plus cyclophosphamide in 104 chemotherapy-naïve women undergoing first-line treatment for advanced or recurrent uterine sarcoma of all pathological subtypes (LMS, MMT, endometrial stromal sarcoma, and other types). Approximately 50% ($n=51$) of patients had MMT and 30% ($n=38$) LMS. The response rate was identical in the two arms for patients with measurable disease (19%). However, rates were not reported separately for LMS and MMT. No significant difference in either progression-free survival (median 5.1 versus 4.9 months, $p=0.22$) or overall survival (median 11.6 versus 10.9 months, $p=0.55$) was detected between the two arms.

Significantly more grade 3 and 4 leukocyte, platelet, and gastrointestinal toxicity were detected for the combination.

The third RCT was a non-blinded, multicentre trial for first- and second-line treatment of advanced or recurrent uterine sarcoma of all pathological subtypes including primarily LMS and MMT (16). Omura et al (16) compared doxorubicin to doxorubicin with DTIC. Patients were allowed to have been exposed to previous chemotherapy but were excluded if they had prior treatment with doxorubicin or DTIC. Two hundred and twenty-six women were eligible. Approximately 52% (n=72) had MMT and 32% (n=48) had LMS. The authors did not indicate how many patients had received prior chemotherapy in each treatment group, nor did they report how many patients with each histologic subtype received prior chemotherapy. The median survival for all LMS patients was longer than that of patients with other cell types (12.1 versus 6.0 months). Patients randomized to doxorubicin plus DTIC had a significantly higher response rate overall ($p < 0.05$), and the trend favouring the combination was seen in both histological subtypes (MMT: 23% versus 10% and LMS: 30% versus 25%). Subgroup analysis of response rates was not reported separately for patients with LMS and MMT. Lung metastases responded more frequently to combination therapy (36% versus 10%, $p = 0.04$) but there was no survival advantage in this subgroup. There was no significant difference between doxorubicin and doxorubicin plus DTIC, in progression-free survival (3.5 months versus 5.5 months) nor in overall survival (7.7 months versus 7.3 months). There was significantly more grade 3 and 4 leukocyte, platelet, and gastrointestinal toxicity in the combination group.

Table 2. Details of randomized controlled trials included in the evidence summary.

Study	1 st or 2 nd line therapy	# of patients	# of patients/arm	Prior treatment	Treatment	Complete response (%)	Partial response (%)	Stable disease (%)	Progress disease (%)	Median PFS (months)	Median survival (months)
Sutton, 2000 (15)	1 st	194	102 MMT ^a	27 RT	1.5 g/m ² IV ifosfamide for 5 days every 3 weeks (course reduced to 4 days because of excess toxicity)	25 (26%)	12 (13%)	36 (38%)	23 (23%)	4.0	7.6
			92 MMT ^a	25 RT	1.5 g/m ² IV ifosfamide + 20 mg/m ² IV cisplatinum for 5 days every 3 weeks (course reduced to 4 days because of excess toxicity)	29 (33%)	21 (24%)	28 (32%)	9 (10%)	6.0 p=0.02	9.4 p=0.07
Muss, 1985 (17)	1 st	89	21 LMS/21MMT	NR	60 mg/m ² IV doxorubicin every 3 weeks	1 (4%)	4 (15%)	14 (54%)	7(27%)	5.1 ^c	11.6 ^c
			17LMS/30 MMT	NR	60 mg/m ² IV doxorubicin + 500 mg/m ² IV cyclophosphamide every 3 weeks	2 (8%)	3 (11%)	13 (50%)	8(31%)	4.9 ^c	10.9 ^c
Omura, 1983 (16)	1 st /2 nd	48	28 LMS	NR	60 mg/m ² IV doxorubicin every 3 weeks	-	7 (25%) ^b	NR	NR	3.5 ^c	7.7 ^c
			20 LMS	NR	60 mg/m ² IV doxorubicin + 250 mg/m ² IV DTIC daily for 5 days every 3 weeks	-	6 (30%) ^b	NR	NR	5.5 ^c	7.3 ^c
Omura, 1983 (16)	1 st /2 nd	72	41 MMT	NR	60 mg/m ² IV doxorubicin every 3 weeks	-	4 (10%) ^b	NR	NR	3.5 ^c	7.7 ^c
			31 MMT	NR	60 mg/m ² IV doxorubicin + 250 mg/m ² IV DTIC every 3 weeks	-	7 (23%) ^b	NR	NR	5.5 ^c	7.3 ^c

Note: DTIC, dimethyl triazenoimidazole carboxamide; IV, intravenous; NR, not reported; PFS, progression-free survival; RT, radiotherapy.

^a Ninety-six patients in the ifosfamide alone group and 87 patients in the ifosfamide with cisplatinum group were evaluable for response.

^b Complete + partial responses

^c Combined PFI and survival for various histologic subtypes of uterine sarcoma

Non-comparative (phase II) studies

With the exception of the three previously described RCTs, published studies of the systemic management of advanced, recurrent, or metastatic uterine sarcoma are non-comparative. Twenty-two prospective phase II studies (18-39) identified were designed to evaluate a specific histologic subtype of uterine sarcoma and examined both first- and second-line treatment scenarios. The major outcomes described are response rate, and less consistently, progression-free interval and median survival. Toxicity data was usually provided, but the majority of the information is related to hematologic and gastrointestinal toxicity. Quality-of-life data was not reported.

Leiomyosarcoma

First Line

Seven prospective phase II trials (18-24) reported response rates of first-line chemotherapy for patients with LMS (Table 3). All studies reported different first-line chemotherapy regimens. Single agent chemotherapy regimens included topotecan, paclitaxel, cisplatin, and etoposide. Combination chemotherapy regimens included doxorubicin plus cyclophosphamide, doxorubicin plus mitomycin plus cisplatin, hydroxyurea plus DTIC plus etoposide, and ifosfamide plus doxorubicin.

Single agent chemotherapy for first-line treatment of advanced LMS showed poor response rates ranging from 0% to 11%. Combination chemotherapy yielded higher response rates ranging from 18% to 30% but were associated with increased toxicity. Unfortunately, none of the studies compare the same treatment regimen; so it is difficult to indicate which treatment regimen is superior to another in terms of response based on the phase II data.

Second Line

Eight prospective phase II studies (25-32) reported the effects of second-line chemotherapy for patients with LMS (Table 3). All eight of the studies reported different second-line chemotherapy regimens. Single agent chemotherapy included amonafide, aminothiadiazole, oral etoposide, diaziquone, paclitaxel, gemcitabine, and oral trimetrexate with response rates ranging from 0% to 21%.

Of the studies investigating single agent chemotherapy, the prospective study by Look et al (25) that studied gemcitabine, reported the highest response rate (21%). Forty-four patients were entered in the study: 35 of the patients (80%) had received previous treatment with chemotherapy, and 11 of the patients (20%) had been previously treated with radiation therapy. This study reports a response rate of 21%, however, it does not indicate the duration of response, nor does it describe results regarding survival for any of the patients.

Hensley et al (29) investigated the combination of gemcitabine (900mg/m² day 1 and 8) plus docetaxel (100mg/m² day 8) given every three weeks. All 34 patients in the study had received previous chemotherapy; 16 of them had received doxorubicin with or without ifosfamide. Nine percent had a complete response rate, 44% had a partial response, and 21% had stable disease. Of the 16 patients who had received previous chemotherapy with doxorubicin, eight had an objective response (50%). The median survival of 17.9 months was longer than that reported in the other first- and second-line phase II trials, but the trial design does not allow for a firm conclusion. In summary, this non-comparative study reported objective response rates greater than 50% and a prolonged median survival of 17.9 months with gemcitabine and docetaxel in patients with LMS.

Table 3. Response rates to various treatments for uterine leiomyosarcoma.

Study	No. of Patients ^a	Prior Treatment	Treatment	Complete Response (%)	Partial Response (%)	Stable Disease (%)	Increasing Disease (%)	Median PFI (months)	Median Survival (months)
<i>First-line chemotherapy</i>									
Currie, 1996 (18)	38	11 RT	2 g oral hydroxyurea; 700 mg/m ² IV DTIC; 300 mg/m ² IV VP-16 every 4 weeks	2 (5%)	5 (13%)	20 (53%)	11 (29%)	NR	15
Edmonson 2002 (19)	35	8 RT	8 mg/m ² IV mitomycin; 40 mg/m ² IV doxorubicin; 60 mg/m ² cisplatinum in 0.45% saline	3 (9%)	5 (14%)	14 (40%)	13 (37%)	NR	6.3
Miller, 2000 (20)	36	8 RT	1.5 mg/m ² IV topotecan for 5 days every 3 weeks	1 (3%)	3 (8%)	12 (33%)	20 (56%)	NR	NR
Sutton, 1999 (21)	33	8 RT	175 mg/m ² IV paclitaxel every 3 weeks	3 (9%)	0	8 (24%)	22 (67%)	NR	NR
Sutton, 1996 (22)	33	9 RT	5 mg/m ² IV ifosfamide every 24 hr; 6 mg/m ² IV mesna every 36 hr; 50 mg/m ² IV doxorubicin every 3 weeks	1 (3%)	9 (27%)	17 (52%)	6 (18%)	NR	NR
Thigpen, 1996 (23)	28	7 RT	100 mg/m ² IV etoposide for 3 days every 3 weeks	0	0	13 (46%)	15 (54%)	2.1	9.2
Thigpen, 1991 (24)	33	8 RT	50 mg/m ² IV cisplatinum every 3 weeks	0	1 (3%)	18 (55%)	14 (42%)	NR	7.8
<i>Second-line chemotherapy</i>									
Asbury, 1998 (26)	26	8 RT 25 CT	300 mg/m ² amonafide for 5 days every 3 weeks	0	1 (4%)	7 (27%)	18 (69%)	NR	NR
Asbury, 1995 (27)	20	NR	125 mg/m ² aminothiadiazole weekly	0	0	5 (25%)	15 (75%)	NR	NR
Gallup, 2003 (28)	48	15 RT 33 CT	175 mg/m ² paclitaxel for 3 weeks	2 (4%)	2 (4%)	11 (23%)	33 (69%)	1.5	12.1
Hensley, 2002 (29)	34	14 RT 16 CT	900 mg/m ² gemcitabine on days 1 and 8 100 mg/m ² docetaxel on day 8 every 3 weeks	3 (9%)	15 (44%)	7 (21%)	9 (26%)	5.6	17.9
Look, 2004 (25)	44	11 RT 35 CT	1000 mg/m ² gemcitabine on days 1, 8, 15 repeated every 28 days	1 (2%)	8 (18%)	7 (16%)	26 (64%)	NR	NR
Rose, 1998 (30)	29	6 RT 27 CT	50 mg/m ² oral etoposide daily for 21 days, every 4 weeks	0	2 (7%)	NR	NR	2.1	7.6
Slayton, 1991 (31)	24	NR	22.5 mg/m ² IV diaziquone every 3 weeks	0	0	8 (33%)	16 (67%)	NR	NR
Smith, 2002 (32)	23	7 RT 10 CT	5 mg/m ² oral trimetrexate for 5 days every other week	0	1 (4%)	11 (48%)	11 (48%)	2.2	7.2

Note: CT, chemotherapy; DTIC, dimethyl triazenoimidazole carboxamide; IV, intravenous; NR, not reported; PFI, progression-free interval; RT, radiotherapy; VP-16, etoposide.

^a Number of patients evaluable for response.

Mixed Mesodermal Tumours

First Line

Two non-comparative studies (24,33) were identified that reported response rates of first-line chemotherapy for mixed mesodermal tumours (Table 4). The studies examined different chemotherapy regimens (cisplatinum or hydroxyurea, etoposide, and DTIC). The response rate (RR) for cisplatinum alone was 19% and 15% for the combined chemotherapy regimen.

Second Line

Five non-comparative studies (34-38) reported the effects of second-line chemotherapy for patients with MMT (Table 4). All five studies reported results on different single agent chemotherapy regimens including amonafide, aminothiadiazone, paclitaxel, diaziquone, and trimetrexate. The studies did not report what previous chemotherapy regimens patients had received. The study by Curtin et al (36) studied the effects of paclitaxel 170mg/m² every three weeks and was the only study to report an objective response rate greater than 10% (RR=18%). Based on the phase II data, it is difficult to establish which systemic treatments are optimal in terms of response rate because the studies all examine various chemotherapy regimens.

Endometrial stromal sarcoma

First Line

There was only one prospective phase II study identified that investigated systemic therapy for patients with advanced, recurrent, or metastatic endometrial stromal sarcomas (39). Twenty-one chemotherapy-naïve patients were treated with ifosfamide (1.5g/m²) daily for five days every three weeks. Three women experienced complete tumour responses (14%), and four women experienced partial tumour responses (19%). The median progression-free interval was three months, and survival was not reported. In this trial, Sutton et al (39) reported a response rate of 33% in the first-line treatment of endometrial stromal sarcomas in women treated with ifosfamide as a single agent. Unfortunately, there was only one small phase II trial identified that examined women with endometrial stromal sarcoma; more studies need to be conducted to support or refute the results reported in this trial.

Table 4. Response rates to various treatments for uterine mixed mesodermal tumours.

Study	No. of Patients ^a	Prior Treatment	Treatment	Complete Response (%)	Partial Response (%)	Stable Disease (%)	Progressive Disease (%)	Median PFI (months)	Median Survival (months)
<i>First-line chemotherapy</i>									
Currie, 1996 (33)	32 (16 hetero)	11 RT	2 g oral hydroxyurea day 1; 700 mg/m ² IV DTIC day 2; 100 mg/m ² IV VP-16 on days 2,3,4; every 4 weeks	2 (6%)	3 (9%)	17(53%)	10 (32%)	6.3	NR
Thigpen, 1991 (24)	63	28 RT	50 mg/m ² IV cisplatinum every 3 weeks	5 (8%)	7 (11%)	32 (50%)	19 (30%)	NR	7.0
<i>Second-line chemotherapy</i>									
Asbury, 1998 (34)	16	5 RT 14 CT	300 mg/m ² IV amonafide for 5 days every 3 weeks	0	1 (6%)	1 (6%)	14 (88%)	NR	NR
Asbury, 1996 (35)	22	10 RT 18 CT	125 mg/m ² IV aminothiadiazole at weekly intervals	0	1 (5%)	NR	NR	NR	NR
Curtin, 2001 (36)	44 (26 hetero)	15 RT 33 CT	170 mg/m ² IV paclitaxel every 3 weeks	4 (9%)	4 (9%)	NR	NR	4.3	NR
Fowler, 2002 (37)	21 (11 hetero)	NR	5 mg/m ² oral TMTX for 5 days every 2 weeks	0	1 (5%)	NR	NR	NR	NR
Slayton, 1991 (38)	23	11 RT 18 CT	22.5 mg/m ² IV diaziquone every 3 weeks	0	1 (4%)	7 (32%)	14 (64%)	NR	NR

Note: CT, chemotherapy; DTIC, dimethyl triazenoimidazole carboxamide; IV, intravenous; NR, not reported; PFI, progression-free interval; RT, radiotherapy; TMTX, trimetrexate; VP-16, etoposide;

^a Number of patients evaluable for response.

Pooled analysis of phase II studies

Given the paucity of survival data available from randomized trials to compare various chemotherapy regimens, the response rates of all phase II studies were pooled to compare the difference in RR between single agent and combination chemotherapy for different histological subtypes (Tables 5 and 6). These kinds of comparisons are fraught with problems, including the use of RR as a surrogate outcome measure, the heterogeneity of the various trial designs and study populations, and the different doses of drugs used. But given the limitations of the available data, a comparison of response rates can provide the reader with a rough estimate of the clinical usefulness of certain drugs. In lieu of stronger data, this may be helpful in making opinion-based recommendations particularly in patients with symptomatic, progressive disease.

For first-line treatment, the pooled overall RR in the phase II trials for patients with LMS was higher in patients treated with combination chemotherapy compared to single agent chemotherapy (22.7% versus 5.8%). In patients with MMT, there was little difference in RR between combination and single agent chemotherapy (15.7% versus 19.0%).

For second-line treatment, the pooled overall RR in the phase II trials for patients with LMS was much higher in patients treated with combination chemotherapy compared to single agent chemotherapy (53.0% versus 7.0%). There were no phase II trials examining second-line combination chemotherapy in patients with MMT, the pooled RR for the single agent chemotherapy for patients with MMT was 6.7%.

Table 5. Results of pooled analysis of phase II trials.

Response rate	RR all histologies (reference)	RR LMS (reference)	RR MMT (reference)
<i>First-line chemotherapy</i>			
Pooled single agents and combination agents	7.9% [95% CI 7.0-8.8%] (18-24,33)	9.9% [95% CI 8.2-11.6%] (18-24)	17.5% [95% CI 14.6-20.4%] (24,33)
Pooled single agents	8.1% [95% CI 7.0-9.2%] (20,21,23,24)	5.8% [95% CI 4.8-6.9%] (20,21,23,24)	19.0% [95% CI 10.3-30.9%] (24)
Pooled combination agents	20.5% [95% CI 17.8-23.2%] (18,19,22,33)	22.7% [95% CI 19.4-26.0%] (18,19,22)	15.7% [95% CI 5.3-32.8%] (33)
<i>Second-line chemotherapy</i>			
Pooled single agents and combination agents	8.2% [95% CI 7.4-9.0%] (25-32,34-38)	9.2% [95% CI 8.9-9.5%] (25-32)	6.7% [95% CI 5.6-7.8%] (34-38)
Pooled single agents	6.9% [95% CI 6.2-7.6%] (25-28,30-32,34-38)	7.0% [95% CI 6.0-8.0%] (25-28,30-32)	6.7% [95% CI 5.6-7.8%] (34-38)
Pooled combination agents	N/A	53.0% [95% CI 35.0-70.0%] (29)	N/A

Note: CI, confidence interval; LMS, leiomyosarcoma; MMT, mixed mesodermal tumour; N/A, not applicable; RR, response rate

Based on this pooled data, it appears that patients who receive first-line chemotherapy for the treatment of metastatic LMS attain a higher RR with combination chemotherapy compared to single agent chemotherapy. No similar trend was noted in first-line treatment for MMT. Although the pooling of this data does not have strong statistical power, and the use of RR as an outcome measure is limited, the results highlight an interesting observation that responses may vary by different histology. Future studies should account for this either by histological stratification or by designing studies targeted to specific histologies.

Table 6. Summary of Response Rates (CR+PR) according to chemotherapeutic regimen.

Chemotherapy	LMS (reference)	MMT (reference)	Endometrial Stromal Sarcomas (reference)
<i>First-line chemotherapy</i>			
Cisplatinium	3% (24)	19% (24)	NA
Doxorubicin	19% ^a (16)	19% ^a (16)	NA
Doxorubicin plus cyclophosphamide	19% ^a (16)	19% ^a (16)	NA
Doxorubicin plus ifosfamide	30% (22)	NA	NA
Doxorubicin plus mitomycin plus cisplatinium	23% (19)	NA	NA
Etoposide	0% (23)	NA	NA
Hydroxyurea plus DTIC plus etoposide.	18% (18)	15% (33)	NA
Ifosfamide	NA	39% (15)	33% (39)
Ifosfamide and cisplatinium	NA	57% (15)	NA
Paclitaxel	9% (21)	NA	NA
Topotecan	11% (20)	NA	NA
<i>Second-line chemotherapy</i>			
Amonafide	4% (26)	6% (34)	NA
Aminothiadiaazole	0% (27)	5% (35)	NA
Diaziquone	0% (31)	0% (38)	NA
Doxorubicin	25% ^b (17)	19% ^b (17)	NA
Doxorubicin and DTIC	30% ^b (17)	23% ^b (17)	NA
Gemcitabine	20% (25)	NA	NA
Gemcitabine plus docetaxel	53% (29)	NA	NA
Oral etoposide	7% (30)	NA	NA
Oral trimetrexate	4% (32)	5% (37)	NA
Paclitaxel	8% (28)	18% (36)	NA

Note: CR, complete response; DTIC, dimethyl triazenoimidazole carboxamide; LMS, leiomyosarcoma; MMT, mixed mesodermal tumour; NA, not available; PR, partial response

^a For all sarcomas

^b Includes first and second-line patients

Toxicity

Toxicity data was generally confined to hematological and gastrointestinal (GI) toxicity. In the three RCTs identified (15-17), combination chemotherapy resulted in increased toxicity compared to single agent therapy. This information is summarized in Table 7a. In the study by Omura et al (16), doxorubicin and DTIC compared to doxorubicin alone resulted in more grade 3 and 4 hematologic (48% versus 20%) and GI toxicity (9% versus 2%).

Sutton et al (15) reported six deaths in the combination arm before the first dose reduction. Four patients died of granulocytopenic sepsis, one complicated by acute renal failure, one died of hemorrhagic stroke with thrombocytopenia, and one of aspiration after severe nausea and vomiting. One also developed acute myelocytic leukemia after eight cycles of treatment, but the relationship of this disease with chemotherapy is unclear. The combination arm had a higher incidence of other adverse events, including granulocytopenia (36% versus 60%), anemia (8% versus 17%) peripheral neurologic symptoms (1% versus 12%), and cardiac symptoms (0% versus 3%) but a somewhat lower incidence of central neurologic symptoms (19% versus 14%) than the single-treatment arm.

Among the phase II trials in first-line therapy, aminothiadiazole, cisplatin, etoposide, and paclitaxel had the fewest adverse effects. This was also true in the second-line setting, although all were associated with more side effects compared to first-line treatment (Tables 7b and 7c).

Table 7a. Grade 3 or 4 adverse effects observed in patients included in the RCTs.

Study	Treatment	Leukopenia	Thrombo- cytopenia	Neutropenia	Anemia	GI	Other
Muss, 1985 (17)	60 mg/m ² IV doxorubicin	5 (10%)	0	NR	NR	NR	0
	60 mg/m ² IV doxorubicin + 500 mg/m ² IV cyclophosphamide	19 (35%)	0	NR	NR	NR	3 (6%) nausea
Omura, 1983 (16)	60 mg/m ² IV doxorubicin	13 (16%)	3 (4%)	NR	NR	2 (2%)	NR
	60 mg/m ² IV doxorubicin + 250 mg/m ² IV DTIC	31 (35%)	11 (13%)	NR	NR	8 (9%)	NR
Sutton, 2000 (15)	1.5 g/m ² IV ifosfamide	59 (59%)	5 (5%)	36 (36%)	8 (8%)	1 (1%)	4 (4%) nausea 1 (1%) hematuria 2 (2%) creatinine elevation 19 (19%) central neurologic symptoms 1 (1%) peripheral neurologic symptoms
	1.5 g/m ² IV ifosfamide + 20 g/m ² IV cisplatinum	87 (97%)	58 (64%)	60 (67%)	17 (19%)	4 (4%)	13 (14%) nausea 3 (3%) creatinine elevation 3 (3%) cardiac 14 (16%) central neurologic symptoms 12 (13%) peripheral neurologic symptoms

Note: DTIC, dimethyl triazenoimidazole carboxamide; GI, gastrointestinal; IV, intravenous; NR, not reported; RCT, randomized controlled trial; VP-16, etoposide.

Table 7b. Grade 3 or 4 adverse effects observed in patients with leiomyosarcoma.

Study	Treatment	Leukopenia	Thrombocytopenia	Neutropenia	Anemia	GI	Other
<i>First-line chemotherapy, LMS</i>							
Currie, 1996 (18)	2 g oral hydroxyurea; 700 mg/m ² IV DTIC; 300 mg/m ² IV VP-16	11 (29%)	1 (3%)	NR	NR	NR	NR
Edmonson 2002 (19)	8 mg/m ² IV mitomycin; 40 mg/m ² IV doxorubicin; 60 mg/m ² cisplatinum	NR	NR	NR	NR	NR	3 (9%) pulmonary toxicity
Miller, 2000 (20)	1.5 mg/m ² IV topotecan	8 (22%)	3 (8%)	28 (78%)	3 (8%)	NR	NR
Sutton, 1999 (21)	175 mg/m ² IV paclitaxel	3 (9%)	1 (3%)	11 (33%)	1 (3%)	NR	1 (3%) allergic reaction
Sutton, 1996 (22)	5 mg/m ² IV ifosfamide; 6 mg/m ² IV mesna; 50 mg/m ² IV doxorubicin	0	0	17 (49%)	0	0	1 (3%) cardiac
Thigpen, 1996 (23)	100 mg/m ² IV etoposide	6 (21%)	1 (4%)	5 (19%)	5 (19%)	0	1 (4%) dermatologic
Thigpen, 1991 (24)	50 mg/m ² IV cisplatinum	2 (2%)	0	NR	NR	NR	NR
<i>Second-line chemotherapy, LMS</i>							
Asbury, 1998 (26)	300 mg/m ² amonafide	12 (46%)	4 (15%)	7 (27%)	3 (12%)	0	1 (4%) neurotoxicity
Asbury, 1995 (27)	125 mg/m ² aminothiadiazole	1 (5%)	NR	1 (5%)	NR	NR	1 (5%) nausea
Gallup, 2003 (28)	175 mg/m ² paclitaxel	3 (6%)	0	8 (17%)	8 (17%)	1 (2%)	1 (2%) fatigue, 1 (2%) pain, 1 (2%) dermatologic, 2 (4%) neurotoxicity, 1 (2%) cardiovascular, 2 (4%) hepatic, 1 (2%) hyperglycemia
Hensley, 2002 (29)	900 mg/m ² gemcitabine; 100 mg/m ² docetaxel	NR	10 (29%)	7 (21%)	5 (15%)	4 (12%) diarrhoea	7 (21%) dyspnea, 2 (6%) neutropenic fever, 7 (21%) fatigue, 2 (6%) neurologic, 1 (3%) DVT, 1 (3%) alopecia, 2 (6%) allergic reaction
Look, 2004 (25)	1000 mg/m ² gemcitabine	12 (27%)	5 (11%)	15 (34%)	3 (7%)	2 (5%)	4 (9%) RBC transfusion, 4 (9%) vomiting, 1 (2%) GU, 2 (4%) neurotoxicity, 1 (2%) SGOT, 2 (4%) dermatologic, 2 (4%) cardiovascular, 2 (4%) pulmonary
Rose, 1998 (30)	50 mg/m ² oral etoposide	8 (24%)	6 (18%)	12 (35%)	4 (12%)	2 (6%)	2 (6%) neurologic, 1 (3%) DVT, 1 (3%) alopecia, 1 (3%) SGOT, 1 (3%) cardiac, 1 (3%) allergic reaction
Slayton, 1991 (31)	22.5 mg/m ² IV diaziquone	9 (38%)	5 (17%)	NR	NR	NR	NR
Smith, 2002 (32)	5 mg/m ² oral etoposide	2 (7%)	1 (4%)	4 (15%)	4 (15%)	1 (4%)	NR

Note: DTIC, dimethyl triazenoimidazole carboxamide ; DVT, deep vein thrombosis; GI, gastrointestinal; GU, genitourinary; IV, intravenous; LMS, leiomyosarcoma; NR, not reported; RBC, red blood cell.

Table 7c. Grade 3 or 4 adverse effects observed in patients with mixed mesodermal tumours.

Study	Treatment	Leukopenia	Thrombocytopenia	Neutropenia	Anemia	GI	Other
<i>First-line chemotherapy, MMT</i>							
Currie, 1996 (33)	2 g oral hydroxyurea; 700 mg/m ² IV DTIC; 100 mg/m ² IV VP-16	8 (24%)	2 (6%)	NR	1 (3%)	1 (3%)	11 (33%) dermatologic 1 (3%) fever
Thigpen, 1991 (24)	50 mg/m ² IV cisplatinum	2 (2%)	0	NR	NR	NR	NR
<i>Second-line chemotherapy, MMT</i>							
Asbury, 1996 (35)	125 mg/m ² IV aminothiadiazole	0	NR	0	1 (5%)	1 (5%)	1(5%) infection 1 (5%) cardiac
Asbury, 1998 (34)	300 mg/m ² amonafide	7 (44%)	3 (19%)	6 (38%)	1 (6%)	2 (12%)	1 (6%) fatigue
Curtin, 2002 (36)	170 mg/m ² IV paclitaxel	14 (30%)	2 (7%)	20 (43%)	4 (9%)	1 (2%)	9 (20%)
Fowler, 2002 (37)	5 mg/m ² oral TMTX	5 (20%)	3 (12%)	4 (16%)	4 (16%)	3 (12%)	5 (20%)
Slayton, 1991 (31)	22.5 mg/m ² IV diaziquone	9 (38%)	5 (17%)	NR	NR	NR	NR

Note: DTIC, dimethyl triazenoimidazole carboxamide; GI, gastrointestinal; IV, intravenous; MMT, mixed mesodermal tumours; NR, not reported; TMTX, trimetrexate; VP-16, etoposide

V. INTERPRETIVE SUMMARY

An evidence-based analysis of the chemotherapeutic options for treatment of advanced, recurrent, or metastatic uterine sarcoma is limited by the absence of an adequate number of well-designed randomized controlled trials. This review identified three small RCTs. Two were published in the 1980's and one more recently in 2000. The rest of the published literature is in the form of phase II studies that were designed to report response rates and toxicity data.

A major limitation of the studies is that most of the reported results pertain to response rates rather than more definitive outcomes such as overall survival, disease-free survival, and quality of life. This limits the confidence with which statements regarding the benefit of treatment can be made.

The early RCTs did not evaluate the different histological subtypes of uterine sarcoma separately. Therefore, outcomes were not consistently reported based on histology and the studies themselves were not adequately powered to detect differences in response rate or survival based on different histological subtypes. The most recent trial by Sutton et al (15) addressed this problem by limiting enrolment to chemotherapy-naïve patients with MMT advanced, recurrent, or metastatic uterine sarcoma.

In this review we have attempted to overcome the limitations imposed by a paucity of randomized controlled trial data by thoroughly examining the phase II trials, by attempting to discuss response rates by histological subtypes, and by pooling comparable trial data. Doing so is clearly hazardous from a statistical point of view, and these results may only be used to generate hypotheses but not to draw definitive conclusions. Bearing in mind the limitations of the available data and the assumptions in the pooling of data, the following conclusions are offered:

1. Based on results from the RCT by Muss et al, for treatment of chemotherapy-naïve patients with advanced, recurrent, or metastatic uterine sarcomas, the response rate for single agent doxorubicin $60\text{mg}/\text{m}^2$ every 3 weeks was 19%. Single agent doxorubicin compared with doxorubicin in combination with either DTIC or cyclophosphamide has shown no benefit in progression-free interval or survival, but there was increased toxicity with combination treatment. Therefore, single agent doxorubicin is reasonable palliative chemotherapy for patients with advanced uterine sarcoma
2. The two most active single agents for first-line treatment of MMT are ifosfamide (RR=39%) and cisplatin (RR=19%). In a randomized controlled trial, the combination of ifosfamide and cisplatin compared to ifosfamide alone resulted in a higher RR (54% versus 39%) and a small increase in progression-free survival (6.0 versus 4.0 months, $p=0.02$), but there was also greater toxicity and no significant improvement in survival.
3. Response rates of 53% with a median survival of 17.9 months were reported in a small phase II study of second-line therapy in patients with LMS treated with the combination of gemcitabine ($900\text{mg}/\text{m}^2$ day 1 and 8) and docetaxel ($100\text{mg}/\text{m}^2$ day 8) every three weeks. Recently, an abstract reported interim results of a retrospective review of 24 patients with sarcoma of various histologies and sites (10 patients with LMS), treated with gemcitabine plus docetaxel (40). Six of ten patients with LMS had a response, and there was an overall response rate of 54%. This treatment represents a promising strategy that requires further research to assess if the high response rate is reproducible and if it translates into an important difference in survival. In the absence of randomized trials, this phase II data provides reasonable evidence that this combination of chemotherapy is a rational option for the second-line treatment of patients with metastatic LMS.
4. One small phase II trial of ifosfamide $1.5\text{g}/\text{m}^2$ daily for five days repeated every three weeks has demonstrated a RR of 33% in first-line treatment of endometrial stromal sarcomas. Based on the limited evidence available on the treatment of endometrial

stromal sarcoma, no specific treatment recommendations for this particular subtype can be offered at this time.

5. The results of a pooled analysis of phase II studies demonstrated, in first-line treatment for LMS, a higher RR with combination chemotherapy compared to single agent chemotherapy. No similar trend was noted in first-line treatment for MMT. Although the pooling of this data does not have strong statistical power, it does highlight an interesting observation that responses may vary by different histology. Future studies should perhaps account for this either by histological stratification or by designing studies targeted to specific histologies.
6. Among the RCTs, combination chemotherapy resulted in significantly more toxicity with little or no benefit in progression-free interval or overall survival. Among the phase II trials, combination chemotherapy was associated with more toxicity than single agent chemotherapy. The combination of gemcitabine and docetaxel is a notable exception with a high response rate and a relatively mild toxicity profile.

VI. ONGOING TRIALS

The Physician Data Query (PDQ) clinical trials database on the Internet (http://www.cancer.gov/clinical_trials/, accessed June 23, 2004) was searched for reports of ongoing trials.

Protocol ID(s)	Title and details of trial
GOG-161, E-G0161	Phase III randomized study of ifosfamide with or without paclitaxel in patients with advanced, refractory, or recurrent carcinosarcoma of the uterus. Accessed April 26, 2004: http://www.cancer.gov/clinicaltrials/view_clinicaltrials.aspx?version=healthprofessional&cdrid=65891&protocolsearchid=886207
GOG-150, E-G150	Phase III randomized study of whole abdominal radiotherapy versus ifosfamide and cisplatin in patients with optimally debulked stage I-IV carcinosarcoma of the uterus. Accessed April 26, 2004: http://www.cancer.gov/clinicaltrials/view_clinicaltrials.aspx?version=healthprofessional&cdrid=63303&protocolsearchid=886214

VII. EXTERNAL REVIEW OF THE EVIDENCE SUMMARY REPORT

Draft Opinions

Based on the evidence reviewed, the Gynecology Cancer DSG drafted the following opinions:

Target Population

This evidence summary applies to women with newly diagnosed advanced, recurrent, or metastatic unresectable uterine sarcomas who are eligible for systemic chemotherapy. The indications for treatment with systemic chemotherapy include relief of symptoms secondary to advanced uterine sarcoma and prolongation of survival.

Opinions of the Gynecology Cancer Disease Site Group

The lack of sufficient high quality evidence precludes definitive recommendations at this time. Instead, the Gynecology Cancer DSG offers the following opinions based on the evidence reviewed:

- The indications for systemic chemotherapy in this population have not yet been clearly defined. There are no trials that compared systemic chemotherapy to best supportive care in women with advanced uterine sarcoma. Also, there are no quality-of-life data available to assess the impact of chemotherapy on these patients. Some phase II and III

trials have reported improvements in median survival with systemic chemotherapy. Since partial and complete responses are reported with systemic chemotherapy, it is reasonable to offer palliative chemotherapy to patients with advanced, unresectable uterine sarcoma who are symptomatic from their disease.

- For first-line treatment of advanced, recurrent, or metastatic uterine sarcoma (all histologic subtypes), single agent doxorubicin given at a dose of at least 60mg/m² every three weeks is a reasonable option for palliative therapy in women who are eligible for chemotherapy.
- The combination of cisplatin and ifosfamide compared to ifosfamide alone in patients with mixed mesodermal tumours resulted in a statistically significant improvement in progression-free survival. However, it was also associated with significant toxicity and therefore patients should be selected carefully based on age, performance status, and co-morbidities.
- Based on response rates, single agent ifosfamide or cisplatin are reasonable choices for first-line treatment of advanced, recurrent, or metastatic uterine mixed mesodermal tumours.
- Gemcitabine combined with docetaxel has shown promising results for patients undergoing second-line therapy for leiomyosarcoma. Further research is required to assess if the high response rates are associated with an important difference in progression-free survival or overall survival. In the absence of randomized trials, this phase II data provides reasonable evidence that this combination of chemotherapy is a rational option for the second-line treatment of patients with progressive, symptomatic metastatic leiomyosarcoma.
- There is insufficient evidence to comment on treatments specifically for endometrial stromal sarcoma.
- There are not enough high-quality randomized controlled trials examining the role of systemic therapy in relation to overall survival and quality of life in patients with advanced, recurrent, or metastatic uterine sarcoma. Such trials would be of benefit to the gynecologic oncology community and the patients they serve. Patients and practitioners should be encouraged to take part in such trials.

Practitioner Feedback

The draft version of this report was reviewed by Ontario practitioners. Any changes made to the report as a result of practitioner feedback are described in the 'Modifications' section below.

Methods

Practitioner feedback was obtained through a mailed survey of 60 practitioners in Ontario (39 medical oncologists, two hematologists, four pathologists and 15 gynecologists). The survey consisted of items evaluating the methods, results, and interpretive summary. Written comments were invited. The practitioner feedback survey was mailed out on March 1, 2004. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Gynecology Cancer DSG reviewed the results of the survey.

Results

Twenty-six responses were received out of the 60 surveys sent (43% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 14 indicated that the report was relevant to their clinical practice and they completed the survey. Results of the practitioner feedback survey are summarized in Table 8.

Table 8. Results of the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	Neither agree nor disagree	Strongly disagree or disagree
The rationale for developing an evidence summary, as stated in the “Choice of Topic” section of the report, is clear.	14 (100%)	--	--
There is a need for an evidence summary on this topic.	12 (86%)	2 (14%)	--
The literature search is relevant and complete in this evidence summary.	13 (93%)	1 (7%)	--
I agree with the methodology used to summarize the evidence.	14 (100%)	--	--
I agree with the overall interpretation of the evidence in the evidence summary.	13 (93%)	1 (7%)	--
The “Opinions of the Disease Site Group” section of this evidence summary is useful.	13 (93%)	--	1 (7%)
An evidence summary of this type will be useful for clinical decision making.	12 (92%)	--	1 (8%)
At present, there is insufficient evidence to develop a practice guideline on this topic.	11 (79%)	--	3 (21%)
There is a need to develop an evidence-based practice guideline on this topic when sufficient evidence becomes available.	13 (93%)	1 (7%)	--

Summary of Written Comments

Two respondents (14%) provided written comments. The main points contained in the written comments were that there is limited evidence on the chemotherapeutic management of metastatic uterine sarcoma, and that it is difficult to offer guidance to practitioners on the subject. One practitioner indicated that the Opinions of the Gynecology Cancer DSG should include the first bullet, however, the practitioner thought that the other bullets were “overstatements of the evidence”.

Modifications/Actions

The Gynecology Cancer DSG acknowledges that there is a lack of evidence, however, felt that an evidence summary to review all of the available evidence was warranted. The Gynecology Cancer DSG was pleased to see that they were not alone in this conclusion: 92% of the practitioners who responded to the survey also felt that an evidence summary on systemic therapy for uterine sarcoma would be useful in clinical decision making.

The comment by the practitioner who suggested that some of the statements in the Opinions section were “overstatements of the evidence” was thoughtfully considered by the Gynecology Cancer DSG. Despite the paucity of evidence, the Gynecology Cancer DSG wanted to offer as much evidence-based guidance as possible. The Gynecology Cancer DSG decided to leave all of the statements in the Opinions, however, they were re-phrased to stress that the Opinions were based on limited evidence.

Practice Guidelines Coordinating Committee Approval Process

The evidence summary report was circulated to members of the PGCC for review and approval. Eight of 14 members of the PGCC returned ballots. Five PGCC members approved the evidence summary report as written, one member approved the evidence summary report with a comment for consideration by the Gynecology DSG. Another member approved the report with modifications required to the report. One member approved the report conditional on the

Gynecology DSG addressing concerns regarding the wording in the first three bullets of the Opinions section. The PGCC member suggested that the bullets in the Opinion section should be re-worded to start with the opinion statement followed by the evidence to support the statement. The member also suggested revising the third bullet in the Key Evidence for clarification.

Modifications/Actions

The first three bullets of the Opinions of the Gynecology Cancer DSG section were revised so that the opinion statement was presented first, followed by the evidence to support the opinion. The third bullet of the Key Evidence was revised for clarity.

VIII. OPINIONS OF THE GYNECOLOGY CANCER DISEASE SITE GROUP

The lack of sufficient high quality evidence precludes definitive recommendations at this time. Instead, the Gynecology Cancer Disease Site Group offers the following opinions based on the evidence reviewed:

- It is reasonable to offer palliative chemotherapy to patients with advanced, unresectable uterine sarcoma who are symptomatic from this disease. This opinion is based on Phase II and III trials that report partial and complete responses and improvements in median survival time with systemic chemotherapy. There are no trials that compare systemic therapy to best supportive care in women with advanced uterine sarcoma, nor are there quality of life data available to assess the impact of chemotherapy on these patients.
- Single agent doxorubicin, given in a dose of at least 60mg/m² every three weeks, is a reasonable option for palliation of women with advanced or metastatic uterine sarcoma, who are eligible for chemotherapy. This opinion is based on the results of two small randomized controlled trials (N=86, N=226) of first-line treatment.
- The combination of cisplatin and ifosfamide is also a reasonable option for women with advanced or metastatic mixed mesodermal tumours, however, this combination is associated with significant toxicity when compared to ifosfamide alone. Therefore, patients should be selected carefully based on age, performance status, and co-morbidities.
- Gemcitabine combined with docetaxel has shown promising phase II study results for patients undergoing second-line therapy for leiomyosarcoma. Further research is required to assess if the high response rates are associated with an important difference in progression-free survival or overall survival. In the absence of randomized trials, this phase II data provides reasonable evidence that this combination of chemotherapy is a rational option for the second-line treatment of patients with progressive, symptomatic metastatic leiomyosarcoma.
- There is insufficient evidence to comment on treatments specifically for endometrial stromal sarcoma.
- There are not enough high-quality randomized controlled trials examining the role of systemic therapy in relation to overall survival and quality of life in patients with advanced, recurrent, or metastatic uterine sarcoma. Such trials would be of benefit to the gynecologic oncology community and the patients they serve. Patients and practitioners should be encouraged to take part in such trials.

IX. JOURNAL REFERENCE

A systematic review based on this guideline has been published in the peer-reviewed journal *Gynecologic Oncology*.

(http://www.elsevier.com/wps/find/journaldescription.cws_home/622840/description#description)

- Kanjeekal S, Chambers A, Fung MF, Verma S. Systemic therapy for advanced uterine sarcoma: a systematic review of the literature. *Gynecol Oncol*. 2005 May;97(2):624-37. An abstract based on the results of this evidence summary was released at the 2004 annual meeting of the American Society of Clinical Oncology:
- Kanjeekal S, Chambers A, Fung Kee Fung M, Verma S. Metastatic uterine sarcoma: a systematic review of the literature [Internet abstract]. *J Clin Oncol*. 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition). 2004;22(Jul 15 Suppl 14S):A706. Available at: http://www.asco.org/ac/1,1003,_12-002636-00_18-0026-00_19-001032,00.asp. Accessed: 2004 Sep 24.

IX. ACKNOWLEDGMENTS

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For a complete list of the Gynecology Cancer Disease Site Group members and the Practice Guidelines Coordinating Committee members, please visit the PEBC section of the CCO Web site at http://www.cancercare.on.ca/access_PEBC.htm.

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Appendix 1. Literature search strategy.

1. random:.sh,pt,tw.
2. controlled:.sh,tw,pt.
3. clinical trial?.sh,tw,pt.
4. prospective stud:.sh,tw,pt.
5. or/1-4
6. exp guidelines/
7. (practice guidelines or guideline?).tw,pt.
8. consensus.sh,tw,pt.
9. or/6-8
10. meta-analysis.sh,pt.
11. (meta-anal: or metaanal: or metanal:).tw.
12. (systematic: review? or systematic: overview?).tw.
13. or/10-13
14. 5 or 9 or 13
15. uter:.tw.
16. leiomyosarcoma/
17. 15 and 16
18. 14 and 17
19. mixed mesodermal tumour/
20. 15 and 19
21. 14 and 20
22. endometrial stromal sarcoma/
23. 14 and 22

Appendix 2. Pathological classification of uterine sarcomas: adopted by the International Society of Gynecologic Pathologists.

Pure Non-Epithelial tumour Classification

- Endometrial Stromal Tumor
 - Stromal nodule
 - Low-grade stromal nodule
 - High-grade stromal nodule
- Smooth-muscle tumors
 - Leiomyoma
 - Cellular
 - Epithelioid
 - Bizarre (symplastic, pleomorphic)
- Lipoleiomyoma
- Smooth-muscle tumor of uncertain malignant potential
- Leiomyosarcoma
 - Epithelioid
 - Myxoid
- Other Smooth Muscle Tumors
 - Metastasizing Leiomyoma
 - Intravenous leiomyomatosis
 - Diffuse leiomyomatosis
- Mixed endometrial stromal and smooth-muscle tumors
- Adenomatoid tumor
- Other soft-tissue tumors (benign and malignant)
 - Homologous
 - Heterologous

Mixed epithelial-nonepithelial tumor classification

- Benign
 - Adenofibroma
 - Adenomyoma
 - Atypical polypoid adenomyoma
- Malignant
 - Adenosarcoma
 - Homologous
 - Heterologous
- Carcinosarcoma (malignant mixed mesodermal tumor; malignant mixed mullerian tumor)
 - Homologous
 - Heterologous
- Carcinofibroma