Role of chemotherapy and biomolecular therapy in the treatment of uterine sarcomas

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Uterine sarcomas are rare, high-risk malignancies. Expert histologic review is important for accurate diagnosis. For high-grade leiomyosarcomas, the risk of recurrence is high after complete resection of uterus-limited disease; however, no adjuvant therapy has been proven to improve survival. Chemotherapy regimens with efficacy in treating advanced uterine leiomyosarcoma include gemcitabine-docetaxel, doxorubicin and ifosfamide. Uterine carcinosarcomas also carry a high risk of recurrence. Adjuvant chemotherapy is a standard approach for completely resected and metastatic carcinosarcoma. Active agents include carboplatin, cisplatin, ifosfamide and paclitaxel.

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Introduction

Uterine sarcomas are a rare, heterogenous group of neoplasms. They vary in histologic appearance, risk of recurrence, and sensitivity to chemotherapy. Expert histologic review and management by clinicians experienced in the care of sarcomas is recommended. Uterine sarcomas may be classified as leiomyosarcomas, carcinosarcomas, endometrial stromal sarcomas, adenosarcomas, and high-grade undifferentiated sarcomas. Carcinosarcoma is considered by some to be a high-risk, de-differentiated variant of endometrial adenocarcinoma.\textsuperscript{1}

Uterine leiomyosarcoma

Chemotherapy for advanced, metastatic leiomyosarcoma

Important clinical studies aimed at identifying active agents in uterine leiomyosarcoma are presented in Table 1. Doxorubicin has been a standard first-line treatment for advanced soft-tissue sarcomas. Other studies have demonstrated the effectiveness of doxorubicin with ifosfamide, cisplatin, and vincristine. More recently, gemcitabine-docetaxel has demonstrated promising activity in treating advanced and metastatic uterine sarcomas.

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Table 1
Agents tested for efficacy in prospective phase II and III trials for uterine leiomyosarcoma.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Agent</th>
<th>Trial design and population</th>
<th>Number of prior regimens</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omura et al., 1983&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Doxorubicin 60 mg/m² with or without DTIC</td>
<td>Phase III, stage III and intravenous uterine sarcomas</td>
<td>0</td>
<td>Doxorubicin (13/80 (16.3%)) Doxorubicin plus DTIC (16/66 (24.2%)) &lt;br&gt; $P &gt; 0.05$ Doxorubicin response 7/28 (25%) of women with measurable uterine leiomyosarcoma</td>
</tr>
<tr>
<td>Muss et al., 1985&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Doxorubicin 60 mg/m² with or without cyclophosphamide 500 mg/m²</td>
<td>Phase III, advanced or recurrent uterine sarcoma (leiomyosarcoma or carcinosarcoma)</td>
<td>0</td>
<td>Doxorubicin (5/26 (19%)) Doxorubicin plus cyclophosphamide (5/26 (19%))</td>
</tr>
<tr>
<td>Sutton et al., 1992&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Ifosfamide 1500 mg/m² × 5 days (1200 mg/m² if prior pelvic radiation)</td>
<td>Phase II</td>
<td>0</td>
<td>10/33 (30.3%)</td>
</tr>
<tr>
<td>Sutton et al., 1996&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Ifosfamide 5 g/m² plus doxorubicin 50 mg/m²</td>
<td>Phase II, uterine leiomyosarcoma, 33 evaluable women</td>
<td>0</td>
<td>9/42 (20%)</td>
</tr>
<tr>
<td>Look et al., 2004&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Gemcitabine 1000 mg/m² days 1, 8, 15</td>
<td>Phase II, uterine leiomyosarcoma</td>
<td>0–1</td>
<td>18/34 (53%)</td>
</tr>
<tr>
<td>Hensley et al., 2002&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Gemcitabine 900 mg/m² over 90 min days 1 and 8 plus docetaxel 100 mg/m² day 8 (25% lower doses if prior pelvic radiation)</td>
<td>Phase II uterine leiomyosarcoma, or non-uterine leiomyosarcoma</td>
<td>0–2</td>
<td>13/48 (27%)</td>
</tr>
<tr>
<td>Hensley, 2008&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Gemcitabine 900 mg/m² over 90 min days 1 and 8 plus docetaxel 100 mg/m² day 8</td>
<td>Phase II, uterine leiomyosarcoma</td>
<td>0</td>
<td>15/42 (36%)</td>
</tr>
<tr>
<td>Hensley, 2008&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Gemcitabine 900 mg/m² over 90 min days 1 and 8 plus docetaxel 100 mg/m² day 8</td>
<td>Phase II, uterine leiomyosarcoma</td>
<td>1</td>
<td>13/48 (27%)</td>
</tr>
<tr>
<td>McMeekin, 2007&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Thalidomide 200–1000 mg daily</td>
<td>Phase II, uterine leiomyosarcoma</td>
<td>1</td>
<td>0/29 (0%)</td>
</tr>
<tr>
<td>Muss, 1990&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Mitoxantrone 12 mg/m²</td>
<td>Phase II, uterine sarcomas</td>
<td>0–1</td>
<td>0/12 (0%)</td>
</tr>
<tr>
<td>Sutton, 2005&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Liposomal doxorubicin 50 mg/m²</td>
<td>Phase II, uterine leiomyosarcoma</td>
<td>0</td>
<td>5/32 (16%)</td>
</tr>
<tr>
<td>Gallup, 2003&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Paclitaxel 175 mg/m² (135 mg/m² for women who have undergone prior pelvic radiation)</td>
<td>Phase II, uterine leiomyosarcoma</td>
<td>0–1</td>
<td>4/48 (8%)</td>
</tr>
<tr>
<td>Sutton, 1999&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Paclitaxel 175 mg/m²</td>
<td>Phase II, uterine leiomyosarcoma</td>
<td>0</td>
<td>3/33 (9%)</td>
</tr>
<tr>
<td>Thigpen, 1991&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Cisplatin 50 mg/m²</td>
<td>Phase II, uterine sarcomas</td>
<td>0</td>
<td>1/33 (3%)</td>
</tr>
<tr>
<td>Thigpen, 1985&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Piperazinedione 50 mg/m²</td>
<td>Phase II, uterine sarcomas</td>
<td>1</td>
<td>1/19 (5%)</td>
</tr>
<tr>
<td>Thigpen, 1996&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Etoposide intravenous 100 mg/m²</td>
<td>Phase II, uterine leiomyosarcoma</td>
<td>0</td>
<td>0/28 (0%)</td>
</tr>
<tr>
<td>Rose, 1998</td>
<td>Etoposide oral 50–60 mg/m²</td>
<td>Phase II, uterine leiomyosarcoma</td>
<td>1</td>
<td>2/29 (7%)</td>
</tr>
<tr>
<td>Miller, 2000&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Topotecan 1.5 mg/m² daily for 5 days</td>
<td>Phase II, uterine leiomyosarcoma</td>
<td>0</td>
<td>4/36 (11%)</td>
</tr>
</tbody>
</table>
sarcoma. In a phase III trial that included women with uterine leiomyosarcoma, carcinosarcoma or other sarcoma, doxorubicin 60 mg/m² was compared with doxorubicin plus the addition of dimethyl triazenoimidazole carboxamide, achieving objective response in 16% of all women enrolled, with response of 25% among those with uterine leiomyosarcoma. The addition of dimethyl triazenoimidazole carboxamide did not significantly improve response rates.² In a separate phase III trial, the addition of cyclophosphamide to doxorubicin did not improve outcomes among 104 evaluable women with uterine leiomyosarcoma, carcinosarcoma or other uterine sarcoma.³ Ifosfamide has single-agent activity, with a response rate of 17.2% (6 out of 35 women treated in a phase II trial).⁴ The combination of doxorubicin plus ifosfamide achieved objective response in 30% of women with uterine leiomyosarcoma. The incidence of grade 3 or 4 neutropaenia was 48%, and one woman died of sepsis.⁵ Gemcitabine was studied in a phase II trial of women with metastatic uterine leiomyosarcoma who had received zero to one prior chemotherapy regimens, and achieved objective response in 20%, with median duration of response being 4.8 months.⁶ Gemcitabine, delivered as a fixed dose-rate infusion, in combination with docetaxel, achieved objective response in 53% of women with leiomyosarcoma of uterine or non-uterine primary who previously underwent zero to two prior cytotoxic regimens.⁷ In two subsequent multi-institution, phase II studies for women with uterine leiomyosarcoma, this regimen achieved objective response in 36% of women who had not undergone prior chemotherapy, and in 27% of women who had undergone one prior chemotherapy treatment.⁸

The Gynecologic Oncology Group has conducted several other phase II trials in uterine leiomyosarcoma to identify active agents. With the exceptions detailed above, the response rates have failed to exceed 10%. Inactive agents include thalidomide, cisplatin, piperazinedione, paclitaxel, etoposide, oral etoposide, trimetrexate, topotecan and mitoxantrone. Liposomal doxorubicin, a formulation of doxorubicin with less risk for cardiotoxicity or alopecia, but with moderate risk for skin toxicity, was tested in a prospective phase II trial for uterine leiomyosarcoma, and achieved a 16% response among women who had undergone prior chemotherapy. Although this response rate is lower than what would be expected with doxorubicin, liposomal doxorubicin may be a treatment option for certain women with co-morbidities that preclude the use of doxorubicin.

Experience with cytotoxic agents tested in soft-tissue sarcoma trials may inform treatment options for women with uterine leiomyosarcoma. Docetaxel was compared with doxorubicin in a randomised phase II trial for advanced soft-tissue sarcoma. Docorubicin achieved objective response in 30% of women, whereas women treated with docetaxel achieved no response.¹¹ Trabectedin is approved for the treatment of soft-tissue sarcomas in Europe, based on objective response rates ranging from 4–17% in a number of phase II trials. In a study comparing two different doses and schedules of trabectedin for advanced liposarcoma or leiomyosarcoma in women who had received zero to two prior regimens, the objective response rate was 5.6% among women with the 24-h infusion schedule, and 1.6% among women with the weekly schedule. In contrast, a retrospective study of 56 women with uterine leiomyosarcoma who had received prior anthracycline treatment reported a response rate of 20% to treatment with trabectedin.²⁷ Results of

<table>
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<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith, 2002¹⁷</td>
<td>Trimetrexate 5 mg/m² daily for 5 days, every 14 days</td>
<td>Phase II, uterine leiomyosarcoma</td>
<td>0–1</td>
<td>1/23 (4%)</td>
</tr>
<tr>
<td>Garcia-Carbonera, 2005²²</td>
<td>Trabectedin 1.5 mg/m² intravenous over 24 h</td>
<td>Phase II, soft-tissue sarcoma</td>
<td>0</td>
<td>6/35 (17%)</td>
</tr>
<tr>
<td>Ferriss, 2010²⁸</td>
<td>Temozolomide, oral, various doses and schedules</td>
<td>Small retrospective study; one prospective</td>
<td>Variable; zero to three prior regimens</td>
<td>2/6 (33%); 2/12 (16%)</td>
</tr>
<tr>
<td>Anderson and Aghajanian, 2005²⁹</td>
<td>Temozolomide, oral, various doses and schedules</td>
<td>Small retrospective study; one prospective</td>
<td>Variable; zero to three prior regimens</td>
<td>2/6 (33%); 2/12 (16%)</td>
</tr>
<tr>
<td>Boyar, 2005³⁰</td>
<td></td>
<td></td>
<td></td>
<td>1/23 (4%)</td>
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DTIC, dimethyl triazenoimidazole carboxamide.
a prospective phase II study of trabectedin using the 24-h infusion schedule in women with uterine leiomyosarcoma and no prior treatment are awaited. Temozolomide has been reported to have activity in soft-tissue sarcomas in small, retrospective studies. In one study, two responses were reported among six women, and two responses were reported among 12 women in another. In a prospective study, temozolomide was combined with thalidomide for advanced leiomyosarcoma, and responses were observed in one out of 23 women (4%).

Biomolecular treatments for uterine leiomyosarcoma

Trials investigating biomolecular treatments for uterine leiomyosarcoma are presented in Table 2. In a phase I/II study, bevacizumab was added to gemcitabine and docetaxel for women with advanced soft-tissue sarcoma who had not undergone prior treatment. Responses were observed in 11 out of 25 women. Important toxicities included bowel perforation, pneumothorax, fatigue, wound dehiscence and haemorrhage. The Gynecologic Oncology Group is conducting a phase III placebo-controlled trial to determine whether the addition of bevacizumab to fixed-dose rate gemcitabine plus docetaxel improves response rates or progression-free survival in advanced uterine leiomyosarcoma.

Bevacizumab was added to doxorubicin for the treatment of advanced soft-tissue sarcoma (11 out of the 17 women had leiomyosarcoma) who had received zero to one prior regimens and had not previously taken anthracycline. Objective response was observed in only two out of 17 women (12%), which is lower than would be expected for response to doxorubicin in this population. Cardiac toxicity was observed in six women.

Multikinase inhibitors that affect the vascular endothelial growth factor pathway have also been investigated. Sunitinib was studied in a phase II trial designed with a dual end point of either objective response or stable disease at 6 months. Sunitinib failed to meet either criterion for activity: objective response was observed in 8.7%, and only four women (17%) remained progression-free at 6 months. Sorafenib was studied in a phase II trial for soft-tissue sarcomas who had received zero to one prior treatment regimens. Among the 37 women in the leiomyosarcoma cohort, objective response was observed in one woman (2.7%). Pazopanib was studied in a phase II study for women with soft-tissue sarcoma who had received zero to two prior regimens. Forty-one women with leiomyosarcoma were evaluated, and response was observed in one woman (2.4%).

Oestrogen receptors and progesterone receptors have been reported to be expressed in 7–71% of uterine leiomyosarcomas providing a rationale for testing aromatase inhibition in these tumours. Case reports have suggested activity. In one retrospective study, 9% of women had objective response, although women in the study had generally been selected for treatment because of small-volume and relatively indolent disease; thus, the outcomes observed cannot be definitively attributed to the aromatase inhibition treatment.

Chemotherapy for adjuvant treatment of completely resected leiomyosarcoma

Although most uterine leiomyosarcomas are limited to the uterus at the time of diagnosis, the risk for disease recurrence is estimated at 50–70%. No prospective, randomised trial has shown a survival benefit to adjuvant therapy. Although retrospective studies have suggested that adjuvant pelvic radiation might improve local control, a randomised phase III trial of adjuvant pelvic radiation compared with observation for women with early stage uterine sarcoma did not show improvement in local control or survival with pelvic radiation among women with leiomyosarcoma.

The Gynecologic Oncology Group conducted a randomised phase III trial of doxorubicin compared with observation for women with uterine leiomyosarcoma or carcinosarcoma. Adjuvant pelvic radiation was permitted at the clinician’s discretion. In the subgroup of women with leiomyosarcoma, recurrences were seen in 44% of women assigned to doxorubicin treatment and in 61% of women assigned to observation (not statistically significant in this small sample). A retrospective, case-control study evaluated recurrence rates among 18 women with uterine sarcoma (13 leiomyosarcomas) who had been treated with adjuvant doxorubicin, cisplatin and pelvic radiation, comparing recurrence rates with those women matched for age and histology who had received only pelvic radiation.
Chemotherapy-radiation group had a recurrence rate of 38%, compared with 72% among women who had only radiation.

In a small prospective study women with completely resected stage I, II, III or IV uterine leiomyosarcoma were enrolled. All women were treated with four cycles of adjuvant fixed-dose rate gemcitabine plus docetaxel. Among all women, 45% remained disease-free at 2 years. Median progression-free survival exceeded 3 years. Because of the efficacy of doxorubicin in advanced leiomyosarcoma, the subsequent study was designed to offer all women four cycles of fixed-dose rate gemcitabine plus docetaxel, followed by four cycles of doxorubicin. Forty-seven women with uterus-limited disease were enrolled. With median follow-up of 27.4 months, 78% of women remained progression-free at 2 years, and median progression-free survival was 39.3 months.

The standard approach to managing completely resected, uterus-limited leiomyosarcoma remains observation. A phase III randomised trial comparing adjuvant chemotherapy to a no-chemotherapy control group is needed.

Uterine carcinosarcoma

Chemotherapy for advanced, measurable carcinosarcoma

Active chemotherapy agents for uterine carcinosarcomas have been identified from phase II trials. Cisplatin is one of the most active agents, with responses in 19% of women treated as first-line treatment and in 18% as second-line treatment. In one study of 18 women, 12 of whom had measurable disease, objective response was seen in five (42%). Ifosfamide is also active. Responses were seen in 32% of women who had undergone no prior treatment and in 18% of women who had received prior platinum treatment. The activity of ifosfamide plus cisplatin was compared with that of ifosfamide
alone in a phase III trial.\textsuperscript{52} Although higher response rates were seen in the combination arm (54\% v 36\%), six treatment-related deaths occurred, and no difference was found in overall survival.

In older trials that enrolled women with any histology uterine sarcoma, doxorubicin had been shown to have modest activity. In a single institution study, however, no responses were observed among nine women with measurable carcinosarcoma treated with high-dose doxorubicin.\textsuperscript{53} Paclitaxel achieved objective response in 18\% of women as second-line treatment.\textsuperscript{54} Paclitaxel plus ifosfamide was compared with ifosfamide in a phase III trial\textsuperscript{55} and achieved higher response rates, longer progression-free and overall survival, establishing paclitaxel-ifosfamide as a reasonable first-line treatment for advanced uterine carcinosarcoma. Paclitaxel plus carboplatin achieved objective response rate in 54\% of women with chemotherapy-naïve, measurable disease,\textsuperscript{56} making this regimen also a reasonable first-line treatment for advanced carcinosarcoma.

Agents with second-line activity against uterine carcinosarcoma are needed. Topotecan achieved response in five out of 48 women (10\%).\textsuperscript{57} Weekly gemcitabine plus docetaxel achieved objective response in only 8\% of women, although most women had received prior taxane treatment.\textsuperscript{58} Etoposide achieved response in only 7\% of women.\textsuperscript{59}

\section*{Chemotherapy for completely resected carcinosarcoma}

Whole abdominal radiation was compared with treatment of three cycles of ifosfamide plus cisplatin as adjuvant therapy for completely resected stage I, II, III, or IV uterine carcinosarcoma.\textsuperscript{60} Women assigned to the chemotherapy arm had a 29\% lower risk for death. The benefit to chemotherapy was seen in all disease stages. This study established adjuvant chemotherapy as a standard approach for completely resected carcinosarcoma of the uterus.

A retrospective study suggested that a similar benefit of adjuvant chemotherapy could be achieved with paclitaxel plus carboplatin.\textsuperscript{61} That study, coupled with the high objective response rates observed with paclitaxel plus carboplatin for advanced measurable disease, provides the rationale for testing paclitaxel plus carboplatin in the adjuvant setting. The current Gynecologic Oncology Group study for completely resected carcinosarcoma is a phase III comparison of ifosfamide plus paclitaxel versus paclitaxel plus carboplatin.

\section*{Biomolecular treatment for uterine carcinosarcoma}

The oral tyrosine kinase inhibitor, imatinib, was studied in a phase II study for women with uterine carcinosarcoma who had received one or two prior regimens.\textsuperscript{62} Only one woman had stable disease, remaining progression-free at 6 months. In the Gynecologic Oncology Group, trials of biomolecular treatments have been designed with a dual end point of either objective response or progression-free survival at 6 months. Results of a Gynecologic Oncology Group thalidomide phase II trial are awaited. The Gynecologic Oncology Group is currently studying pazopanib in a phase II trial. A separate research group tested thalidomide in women with gynecologic sarcomas, including carcinosarcomas, with the primary end point of progression-free survival.\textsuperscript{63} No responses were reported, and median progression-free survival was less than 2 months (Table 3).

\section*{High-grade undifferentiated uterine sarcoma}

\subsection*{Role of chemotherapy for advanced, metastatic disease}

High-grade undifferentiated uterine sarcomas had previously been called high-grade endometrial stromal sarcomas. No prospective clinical trials have been conducted specifically for high-grade undifferentiated uterine sarcomas. Case reports have been published on responses to doxorubicin and ifosfamide-based treatment.\textsuperscript{64,65} Women with high-grade undifferentiated sarcomas should be encouraged to participate in clinical trials for soft-tissue sarcomas.
Uterine sarcomas with a limited role for chemotherapy

Adenosarcomas without sarcomatous overgrowth and endometrial stromal sarcomas

Certain uterine sarcomas (endometrial stromal sarcomas and adenosarcomas without sarcomatous overgrowth) are low-grade malignancies for which cytotoxic chemotherapy is unlikely to be beneficial. Although distant metastatic disease may be present in 15–30% of women with endometrial stromal sarcomas,66 the 5-year overall survival may exceed 90%;67–69 owing to the indolent behaviour of this cancer. Endometrial stromal sarcomas are often oestrogen-receptor, progesterone-receptor positive, or both. Reports have been published of responses to hormonal treatments with megestrol or aromatase inhibitors.70–76 Adenosarcomas without sarcomatous overgrowth are similarly indolent in behaviour. In these cancers, a benign epithelial component exists together with a malignant stromal component that resembles low-grade endometrial stromal sarcoma. Hormonal treatments are sometimes used for advanced, recurrent adenosarcomas without sarcomatous overgrowth.

Conclusion

Uterine sarcomas are rare malignancies that differ in histologic appearance and in clinical behaviour. Expert histologic review is recommended to guide management. Uterine leiomyosarcomas have
a high risk of recurrence after resection of uterus-limited disease but no adjuvant therapy has been proven to prolong overall survival. Active agents in metastatic uterine leiomyosarcoma include gemcitabine, fixed-dose rate gemcitabine plus docetaxel, doxorubicin and ifosfamide. Uterine carcinosarcomas also have a high risk for recurrence. Adjuvant dual-agent chemotherapy is a standard approach to treatment of completely resected uterine carcinosarcomas. Active agents in uterine carcinosarcoma include carboplatin, cisplatin, paclitaxel, and ifosfamide. Targeted, biomolecular agents are under investigation for uterine leiomyosarcoma and carcinosarcoma.

**Practice points**

- Adjuvant chemotherapy for completely resected uterine leiomyosarcoma remains investigational.
- Adjuvant chemotherapy is a standard treatment after resection of all stages of uterine carcinosarcoma.
- Active chemotherapy regimens for unresectable uterine leiomyosarcoma include doxorubicin with or without ifosfamide, gemcitabine, fixed-dose rate gemcitabine plus docetaxel.
- Active chemotherapy regimens for uterine carcinosarcoma include ifosfamide plus cisplatin ifosfamide plus paclitaxel, and carboplatin plus paclitaxel.

**Research agenda**

- The role of adjuvant chemotherapy in completely resected, uterus-limited leiomyosarcoma should be addressed in a prospective phase III trial with a no-chemotherapy control arm in order to determine whether chemotherapy can improve progression-free, overall survival, or both.
- Correlative science studies will hopefully elucidate molecular and genetic targets that are altered in uterine sarcomas, permitting the development of effective, targeted therapies.

**References**


