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The role of adjuvant therapy in uterine leiomyosarcoma

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Summary

Uterine leiomyosarcoma (uLMS) is a rare mesenchymal tumor of the gynecologic tract. Although diagnosed in only 1-3% of patients with uterine cancer, uLMS accounts for the majority of uterine cancer-related deaths. The standard of care for patients with uLMS includes total hysterectomy and bilateral salpingo-oophorectomy (BSO). There are no standard recommendations regarding adjuvant or palliative therapy. Many cytotoxic and targeted agents have been studied in clinical trials in an effort to identify an effective therapy that may alter the natural history of this disease. Unfortunately, as of now, there are no adjuvant therapy regimens that improve overall survival in this patient population. There is, therefore, an unmet need to identify a novel therapy that will improve the survival of women diagnosed with this aggressive disease. The current review aims to summarize the existing literature on adjuvant therapy in uLMS, specifically highlighting advances made in the last 5 years.

Keywords

uterine leiomyosarcoma; gemcitabine; docetaxel; pazopanib; trabectedin; doxorubicin; ifosfamide; mTOR inhibitor

Introduction

Uterine leiomyosarcoma (uLMS) is a rare malignancy of the gynecologic tract, accounting for 1-3% of all uterine malignancies in the United States and approximately 30% of uterine sarcomas [1, 2]. Total hysterectomy remains the standard of care when uLMS is suspected. Other treatment modalities, including chemotherapy, radiation therapy, and more recently, targeted biologic agents, have also been utilized to treat disease in either the upfront or recurrent setting. This article will review the existing treatment options available for the treatment of uLMS.

When diagnosed at an early stage, women with uterine-confined disease can often be treated with surgery alone and have relatively good 5-year overall survival (OS) rates [3]. On the other hand, women with advanced disease have a more dismal prognosis. According to data from the Surveillance, Epidemiology, and End Results (SEER) Program, which looked at

women with uterine sarcoma between 2004 and 2010, the 5-year relative survival rate for women with localized disease is 63%, compared with 36% and 14% for regional and distant spread, respectively [4]. And although patients with early-stage disease have a favorable prognosis compared with patients with advanced-stage disease, these women still have a high recurrence rate (50-80%) at 2 years after diagnosis [5]. There are few effective therapies to treat these women, and standard treatment options are not clearly defined. Although a variety of treatment modalities have been studied in uLMS, no agent has improved survival, warranting the need for the development of more effective therapies.

Surgical resection

Total hysterectomy with or without bilateral salpingo-oophorectomy (BSO) is the standard treatment for patients with uterine-confined disease. Patients with suspected or confirmed uLMS should have their uterus removed en bloc, with maximal effort to avoid intraoperative rupture, morcellation, or spillage of tumor into the peritoneal cavity. For women with unresectable disease, localized or systemic treatment options are limited. Premenopausal women diagnosed with this disease may be treated with hysterectomy alone. An observational study using SEER data examined women who did and did not have routine BSO at the time of hysterectomy. Women who had BSO had compromised survival [6]. The reason for this is unclear; however there does not appear to be a clear need for BSO in premenopausal women.

Surgical cytoreduction for leiomyosarcoma

When feasible, surgical resection for uLMS should be performed in the appropriately selected patient. Patients with both intraperitoneal and extraperitoneal disease are considered appropriate candidates for surgical resection, despite having metastatic disease. Patients with no residual disease after surgical resection have an improved survival compared to patients with a suboptimal surgical resection [7]. In a retrospective review of all surgical patients with uLMS at Memorial Sloan Kettering Cancer Center, Leitao et al found that an optimal surgical resection was associated with an improved progression-free survival (PFS) of 14.2 months (range, 11.4-16.9) compared with 6.8 months (range, 4.1-9.5) for patients with residual disease ($P=0.002$) [8].

Patients with extraperitoneal disease should also be considered for resection, as women with isolated pulmonary metastases have had improved outcomes following metastasectomy. Several groups have summarized their experience with pulmonary metastasectomy in patients with gynecologic malignancies [9-14]. Pulmonary wedge resection was the preferred method of resection [11]. Five- and 10-year survival rates after pulmonary metastasectomy in this study were 37.9-46.8% and 34.3%, respectively [11, 13]. In these studies, the number of pulmonary nodules on preoperative imaging (>3 nodules), a disease-free interval of less than 12-24 months, and tumor size >3 cm adversely impacted survival [9, 10, 12-15]. Overall, the authors of these studies concluded that pulmonary metastasectomy is an effective option for appropriately selected patients with metastatic uLMS.

Adjuvant radiation therapy

Adjuvant radiation therapy is not routinely recommended in patients with uLMS. In the only randomized study investigating the effects of adjuvant radiation therapy in patients with uLMS, European Organisation for Research and Treatment of Cancer (EORTC) trial 55874 concluded that radiation therapy did not improve local or distant progression rates and had no impact on survival [16]. An observational study utilizing SEER data confirmed that the use of radiation therapy in the adjuvant setting does not improve survival (hazard ratio 1.1; 95% CI, 0.9-1.4) [17].

Systemic therapy

Administration of adjuvant therapy after hysterectomy for patients with high-risk uterine-confined disease has not been shown to alter outcome in the few trials that have been conducted. There is also no proven benefit of chemotherapy for completely resected advanced-stage disease, although it is commonly considered. Doxorubicin, with or without other agents, has been used for years as a proven regimen, with a response rate of approximately 30% in patients with measurable disease [18-20]. More recently, the combination of gemcitabine and docetaxel (with granulocyte colony stimulating factor [G-CSF]) has become the favored regimen, with response rates ranging from 27-53% and an acceptable toxicity profile in patients with measurable disease [21-27].

In the 1970s and 1980s, investigators with the Gynecologic Oncology Group (GOG, now part of NRG Oncology) evaluated the efficacy of Adriamycin in the adjuvant setting in patients diagnosed with stage I or II uterine sarcomas [18, 19]. Patients were randomly assigned to receive treatment with Adriamycin (60mg/m² intravenous every 3 weeks for a total of 8 weeks) or observation alone [18]. Radiation therapy was optional [18]. Overall, 225 patients enrolled on the study from 1973-1982. Seventy-five patients were randomized to the Adriamycin arm and 81 patients were randomized to the observation arm. Of the evaluable cases, 48 patients had leiomyosarcoma, and 25 (52.1%) received treatment with Adriamycin. Eleven patients (11/25; 44%) with leiomyosarcoma who received Adriamycin developed recurrent disease, while 14 patients (14/25; 61%) on the observation arm recurred; this was not statistically different. Adjuvant Adriamycin did not improve PFS or OS. Median survival was 55.0 and 73.7 months for the control and chemotherapy arms, respectively. Among the patients who received radiation therapy prior to receiving chemotherapy, no alteration in survival was observed (Table 1) [18].

Recently, the French Sarcoma Group published findings from the SARCGYN study, which examined the efficacy of doxorubicin, ifosfamide, and cisplatin (API) combined with radiation therapy versus radiation therapy alone as adjuvant therapy in patients with uterine sarcomas. In this study, patients with early-stage uterine sarcoma (leiomyosarcoma, carcinosarcoma, and endometrial stromal sarcoma) were randomly assigned to either a combined chemotherapy (API) and radiation therapy arm or radiation therapy alone. Patients randomized to the combined chemotherapy and radiation therapy arm had improved 3-year disease-free survival (DFS) (55% vs 41%; P=0.048), but no improvement in 3-year OS (81% vs 69%; P=0.41). Though the primary endpoint of the study was met (improvement in 3-year

DFS), the combined chemotherapy and radiation therapy arm was associated with increased toxicity, including 2 deaths (Table 1) [28].

Another study investigating multimodal treatment with the three-drug API regimen for advanced or metastatic uLMS demonstrated efficacy of this regimen either alone or in combination with other therapies, including surgery, radiation therapy, or radiofrequency ablation. The findings of this study corroborated with those of earlier studies that demonstrated this drug combination is effective, albeit with significant associated toxicity. The objective response rate (ORR) was 48%, with 4 complete responses (CRs) and 12 partial responses (PRs) observed [29].

Combination doxorubicin and ifosfamide was first shown to have an improved ORR compared to single-agent therapy in patients with chemotherapy-naïve unresectable uLMS. In this phase 2 clinical trial that enrolled 35 patients, GOG investigators observed 9 PRs (27.3%) 1 CR (3.0%), with an ORR of 30.3%. Stable disease was noted in 17 patients (51.7%). Median duration of response was 4.4 months in those with PRs and 8.7 months in the single patient with a CR [30].

EORTC trial 62012, a phase 3 randomized controlled trial compared single-agent doxorubicin to doxorubicin plus ifosfamide in patients with locally advanced, unresectable, or metastatic high-grade soft tissue sarcoma [31]. Four hundred fifty-five patients were randomly assigned in a 1:1 fashion to doxorubicin (N=228) or doxorubicin plus ifosfamide (N=227). In this study, 103 patients had leiomyosarcoma (54 in the doxorubicin group and 59 in the doxorubicin-ifosfamide arm). Ultimately, OS did not differ between the groups (doxorubicin arm: 12.8 months [95.5% CI, 10.5-14.3] versus doxorubicin-ifosfamide arm: 14.3 months [95.5% CI, 12.5-16.5]; HR, 0.83; 95.5% CI, 0.67-1.03). Median PFS, however, was significantly higher (7.4 months vs 4.6 months), and more patients had an overall response (26% vs 14%; $P<0.0006$) in the combined doxorubicin-ifosfamide arm [31].

Gemcitabine and docetaxel

Numerous studies have been performed examining the efficacy of the combination regimen gemcitabine and docetaxel in patient with uLMS. Both single-institution and collaborative group studies have demonstrated moderate objective response rates, with acceptable toxicity profiles reported in the gynecologic and soft tissue sarcoma literature. Generally a well-tolerated regimen, with the most common side effects including myelosuppression (neutropenia, anemia, thrombocytopenia), fatigue and edema, the combination of gemcitabine plus docetaxel is an acceptable regimen for uLMS [22-25, 27].

Adjuvant trials—Few studies have looked at the combination regimen of gemcitabine-docetaxel in the adjuvant setting (Table 2) [24, 27]. Results of a prospective, single-institution evaluation investigating the efficacy of the combination regimen of gemcitabine plus docetaxel in patients with completely resected uLMS demonstrated an excellent PFS of 13 months in all patients [24]. In that study, patients with completely resected stage I-IV disease were given 4 cycles of gemcitabine-docetaxel. Impressively, patients with stage I or II uLMS had a 2-year PFS rate of 59% and a median PFS of 39 months.

The Sarcoma Alliance for Research through Collaboration (SARC) 005 study—a single-arm, phase 2 trial—prospectively evaluated patients with high-grade uterine-confined leiomyosarcoma (1988 International Federation of Gynecology and Obstetrics [FIGO] stage I, II, or serosa-limited IIIA disease) assigned to receive gemcitabine-docetaxel followed by doxorubicin as a front-line regimen. All patients had a hysterectomy performed, with no evidence of disease on a baseline CT scan. Patients on study were not permitted to receive radiation therapy. Fixed dose rate gemcitabine and docetaxel (with G-CSF support) were administered every 21 days for a total of 4 cycles. After cycle 4, patients underwent repeat imaging with CT scan of the chest, abdomen, and pelvis to confirm no evidence of disease. Patients who had no evidence of disease after 4 cycles of gemcitabine-docetaxel then received doxorubicin every 21 days for an additional 4 cycles. Forty-seven patients were enrolled, and 46 patients were evaluated for both PFS and OS at 2 and 3 years. After a median follow-up of 39.8 months, 78% (95% CI, 67-91%) remained progression free at 2 years and 57% (95% CI, 44-74%) remained progression free at 3 years. Median PFS and OS had not been reached at the time of publication [27]. These data are promising for patients with uLMS with high-risk features in the adjuvant setting. A phase 3 study conducted within the NRG Oncology Group comparing this chemotherapy regimen to observation is currently accruing. The results of this trial are highly anticipated.

Recurrent/advanced setting—The efficacy of the combination regimen gemcitabine-docetaxel in patients with recurrent or advanced uterine leiomyosarcoma has also been studied in several clinical trials (summarized in Table 3) [22, 23, 25, 26, 32, 33]. Originally studied in a single-institution phase 2 clinical trial, the combination of gemcitabine and docetaxel achieved an ORR of 53% (95% CI, 35%-70%) [25]. In that study, patients with unresectable uLMS who had failed on treatment with 0-2 prior chemotherapy regimens were enrolled. Of the 34 patients enrolled, 29 patients had uLMS and 5 patients had LMS of other primary sites. CR was achieved in 3 patients (8.8%), and a PR was observed in 15 (44.1%), for an ORR of 53% (95% CI, 35-70%). Seven patients (20.9%) had stable disease. Sixteen patients had previously received treatment with doxorubicin; and 8 (50%) of these patients had an objective response to the combination of gemcitabine and docetaxel. Two of the patients with CRs had received doxorubicin-based chemotherapy. The median PFS was 5.6 months (95% CI, 4.3- 9.9 months). Forty-seven percent of patients were progression free at 6 months (95% CI, 32- 68%) [25].

The same combination of fixed-dose rate (FDR) gemcitabine and docetaxel was studied as a first-line therapy for patients with metastatic uLMS in a multi-site phase 2 clinical trial performed by the GOG [23]. Forty-two patients accrued to the study, but only 39 patients were evaluable for objective response. Two (4.8%) CRs, 13 (31.0%) PRs, and 11 (26.2%) patients with stable disease were noted. The overall objective response rate was 35.8%. Median PFS was 4.4 months (range, 0.4-37.2 months) and median OS was 16+ months (range, 0.4-41.3 months).

In another phase 2 trial conducted by the GOG, 48 patients with unresectable uLMS received FDR gemcitabine and docetaxel as second-line therapy [22]. Women on that study had unresectable uLMS and were permitted to have had prior cytotoxic therapy. In the multicenter study, the overall objective response rate was 27% (95% CI, 15.3-41.8%); a CR

was seen in 6.3% of patients, and a PR was seen in 20.8%. Twenty-four patients (50%) had stable disease. Median PFS was greater than 5.6 months (range, 0.7-27.0+ months). The median duration of response was greater than 9 months (range, 39-24.5+ months). Median PFS for all 48 patients was 6.7+ months (range, 0.7-27+ months). The PFS rate at 12 weeks was 73% (95% CI, 58.2-84.7%) and 52% (95% CI, 37.2-66.7%) at 24 weeks. Median OS was 14.7 months (range, 0.8-50.9+ months).

Recently, the NRG/GOG investigated whether the addition of the angiogenesis inhibitor bevacizumab to the FDR gemcitabine and docetaxel combination regimen would improve PFS in patients with measurable disease. Results from a phase 1B study of gemcitabine-docetaxel plus bevacizumab for patients with chemo-naïve soft tissue sarcoma had previously demonstrated an objective response rate reaching 31%, with a median duration of response of 6 months [34].

In the NRG/GOG phase 3 randomized, placebo-controlled clinical trial, 107 chemo-naïve patients with metastatic, unresectable disease were randomized to either gemcitabine-docetaxel plus placebo (n=54) or gemcitabine-docetaxel plus bevacizumab (n=53) [26]. The addition of bevacizumab to the standard backbone of gemcitabine-docetaxel did not improve survival. Objective responses were observed in 17 patients (31.5%) in the gemcitabine-docetaxel plus placebo arm and 19 patients (35.8%) in the gemcitabine-docetaxel plus bevacizumab arm [26]. Median PFS was 6.2 months and 4.2 months, in the placebo and bevacizumab arms respectively (HR, 1.12; P=0.58). Median OS was 26.9 months and 23.3 months, respectively (HR, 1.07; P=0.81) [26].

Single-agent therapy

Many other agents have been studied in patients with refractory or recurrent uLMS, but almost none in the adjuvant setting. Single agents that exhibited varying objective responses include gemcitabine [35], docetaxel, pegylated doxorubicin [36, 37], ifosfamide [38], doxorubicin [18], dacarbazine, etoposide [39, 40], temozolomide [41-43], and paclitaxel [44]. Studies conducted in the recurrent setting that did not demonstrate any benefit included cisplatin [45, 46], topotecan [47], pegylated liposomal doxorubicin [37], thalidomide [48], and mifepristone [49].

Gemcitabine, as a single agent, has shown good responses in the recurrent setting. Look et al. conducted a phase 2 trial through the GOG investigating the efficacy of single-agent gemcitabine. Patients enrolled onto the study were allowed to have had either prior chemotherapy (0-1 prior regimens) or radiation therapy. Gemcitabine was delivered at a rate of 1000 mg/m² IV over 30 minutes on days 1, 8 and 15, and cycles were repeated every 4 weeks. One patient (2.3%) achieved a CR and 8 patients (18.2%) achieved a PR, with a combined ORR of 20.5%. The median duration of response was 4.9 months. Seven patients (15.9%) maintained stable disease.

In a randomized phase 2 study comparing single-agent gemcitabine with combination gemcitabine-docetaxel (TAXOGEM study) as second-line therapy in patients with metastatic LMS, investigators reported ORRs of 19% and 24%, respectively, and did not identify a statistical difference in PFS rates at 12 and 24 weeks in patients with uLMS. In this study,

one CR was noted in the single-agent gemcitabine arm among patients with uLMS, but none were observed in the gemcitabine-docetaxel arm. Although patients with uterine and non-uterine LMS were included in this study, patients were stratified by disease site and the authors observed that patients with uLMS may have more chemosensitive disease [32].

Eribulin mesylate is a new agent recently studied in a randomized clinical trial, Study 309, which compared its efficacy to dacarbazine in patients with advanced soft tissue sarcoma. Ultimately, when compared to treatment with dacarbazine, eribulin mesylate improved OS by 2 months (13.5 vs 11.5 months, hazard ratio 0.768; 95% CI, 0.618-0.954; $P=0.0169$). No difference was seen in PFS. This is the first study to demonstrate an improvement in OS in this patient population. Although this study looks at patients with both leiomyosarcoma and adipocytic sarcoma who had failed treatment with prior regimens, these data are encouraging and deserve future exploration [50].

Hormone therapy

Aromatase inhibitors (AIs) are not routinely used in the treatment of uterine LMS. However, estrogen and progesterone receptor (ER and PR, respectively) expression has been identified in 40-80% of human uLMS tumors. Previous studies have shown that patients with PR-expressing tumors may have an improved survival [51]. Several case reports and case series suggest that treatment with an AI as either a consolidation or salvage agent may provide some benefit. AIs are generally well tolerated, with the most common observed toxicities being asthenia, bone pain, arthralgia, and weight gain.

Two separate single-institution case series summarize their experience with AIs in the treatment of uLMS. Between 1998 and 2008 at Memorial Sloan Kettering Cancer Center, O'Cearbhaill et al identified 43 patients who had undergone treatment for uLMS with an AI. PFS was the primary endpoint of that retrospective evaluation. Of the 39 evaluable patients, 34 patients had measurable disease when started on hormone therapy with an AI, and the majority (29/34, 85%) had high-grade disease. Letrozole was the most commonly prescribed agent (74%), at a dose of 2.5 mg orally daily. Although no patient achieved a CR, 3 patients (9%) achieved a PR and 11 patients (32%) had stable disease. The duration of response ranged from 5-12.5 months in the 3 patients with a PR and 13 months in patients with SD (95% CI, 3.1-40.3 months) [52]. Patients with ER- and/or PR-positive disease had longer PFS than patients whose tumors did not express these hormone receptors. Median PFS for all patients was 2.9 months (95% CI, 1.8-5.1 months).

Thanopoulou and colleagues performed a similar retrospective study, identifying 29 patients with uLMS at their institution who were treated with an AI. Only 16 patients were evaluable for analysis in this study and of these only 8 met Stanford criteria for high-grade disease. Letrozole was administered as first-line and exemestane was administered as second-line therapy [53]. No CR was observed, but 2 patients (12.5%) had a PR (1 patient each with low-grade and high-grade disease). Stable disease was noted in 10 patients (62.5%), with 8 patients maintaining a response for >6 months. Six of the 10 patients who maintained stable disease had low-grade uLMS. In the second line of treatment, 3 patients had stable disease as best response. All patients had high-volume but low-grade disease.

In a single-arm phase 2 trial, letrozole (2.5 mg daily) was administered to pre-treated patients with unresectable uLMS who had confirmed ER and/or PR expression. Twenty-seven patients were enrolled on the study, and stable disease was noted in 14 patients (54%; 90% CI, 36-71%), with a median duration of response of 2.2 months (range, 0.4-9.9 months). The 12-week PFS rate was 50% (90% CI, 30-67%). Patients with ER- or PR-expressing tumors had the longest sustained response to treatment with AI therapy. Since the 12-week PFS rate exceeded the 40% PFS rate chosen based on EORTC criteria, letrozole was considered an active agent [54].

Trabectedin

Trabectedin, (ET-743), has cytotoxic, immunomodulatory, and antiangiogenic properties. Indicated for the treatment of patients with advanced soft tissue sarcoma after failure with standard cytotoxic therapies, this drug also has modest activity in leiomyosarcoma. Although not yet approved in the United States, in clinical trials, trabectedin has demonstrated a reasonable response rate in the treatment of LMS.

In 2006, a case report described the clinical course of a patient with recurrent uLMS refractory to multiple cytotoxic regimens who ultimately achieved a PR and stable disease after treatment with 8 cycles of trabectedin (administered at a dose of 1.5 mg/m² IV and then 1.2mg/m² IV) [55]. Since this publication, multiple clinical trials have examined the utility of trabectedin in patients with soft tissue sarcoma, as well as uLMS, with promising results.

Phase 2 data from the French Sarcoma Group (LMS-02) examined the combination of doxorubicin and trabectedin as a first-line treatment regimen in patients with advanced and unresectable uterine or soft tissue leiomyosarcoma. This study revealed an improvement in objective response [56]. The drug combination was well tolerated, with 68% (32/47) patients completing all 6 cycles of treatment and only 5 patients (11%) discontinuing therapy secondary to drug toxicity. Forty-one patients (41/47; 87.2%; 95% CI, 74.3-95.2) with uLMS achieved disease control. No complete responses were observed; however, 28 PRs (59.6%, 44.3-73.6) were noted, and 13 patients (27.7%, 15.6-42.6) maintained stable disease [56]. Twelve-week and 24-week PFS rates were 87.2% (95% CI, 75-94%) and 72.3% (95% CI, 58-84%), respectively. Median PFS was 8.2 months (95% CI, 7.0-9.0). With a median follow-up of 9.9 months (interquartile range (IQR), 6.1-21.5), median OS was 20.2 months (95% CI, 15.1-not reached). Investigators concluded that this drug combination could be an active first-line regimen for both uterine and soft tissue leiomyosarcoma.

The GOG performed a phase 2 trial (GOG 87M) investigating the safety and efficacy of trabectedin, as a single agent, in patients with chemonaïve, unresectable, and advanced uLMS. Patients received a 24-hour IV infusion of single-agent trabectedin at a dose of 1.5 mg/m². Cycles were repeated every 3 weeks and continued until progression of disease, withdrawal of consent, or unacceptable toxicity. Two PRs (2/20, 10%; 95% CI, 1.2-31.7%) were observed, and 10 patients (50%) had stable disease. The median PFS was 5.8 months, and the median OS was greater than 26.1 months [57]. Though the drug did not meet the required response criteria to move on to a second stage, the delay in progression of disease

was considered clinically relevant [57]. A phase 2 trial comparing the combination regimen gemcitabine-docetaxel to single-agent trabectedin is ongoing (NCT 02249702).

Targeted agents

Pazopanib is a multi-kinase angiogenesis inhibitor that targets vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). Patients with recurrent uterine leiomyosarcoma who have failed treatment with prior chemotherapy regimens are candidates for treatment with this drug. Studies in soft tissue sarcoma have demonstrated the efficacy of this agent in patients with leiomyosarcoma, synovial sarcoma, and others. A phase 2 clinical trial demonstrated the safety and efficacy of this angiogenesis inhibitor in patients in three of four cohorts, including the leiomyosarcoma group. Progression-free rates at 12 weeks were greater than 40% in patients with all-site leiomyosarcoma, suggesting efficacy [58].

The PALETTE trial, a phase 3 randomized, double-blind, placebo-controlled study investigated the impact of pazopanib on PFS in patients with advanced, measurable non-adipocytic soft tissue sarcoma. Three hundred seventy-two patients were enrolled, and 369 patients were randomized (2:1) to receive either pazopanib (n=246) or placebo (n=123). All patients had previously failed treatment with chemotherapy. Patients received oral pazopanib 800 mg daily or placebo. Median PFS was 4.6 months (95% CI, 3.7-4.8) for the pazopanib arm versus 1.6 months (95% CI, 0.9-1.8) for the placebo arm (HR, 0.31; 95% CI, 0.24-0.40; $P<0.0001$). And although OS was not significantly altered (HR, 0.86; 95% CI, 0.67-1.11; $P=0.25$), it was felt that pazopanib is a worthy treatment option for patients with metastatic soft tissue sarcoma [59].

Ixabepilone, a semi-synthetic analog of epothilone B, binds to the same site on beta-tubulin as paclitaxel. Ixabepilone was studied by the NRG Oncology Group in a phase 2 trial and found not to be active as a single agent in uLMS [60]. Of 23 evaluable patients enrolled on the trial, only 4 patients (17.4%) had stable disease as best response to therapy.

Neither sunitinib malate nor sorafenib, both multi-targeted tyrosine kinase inhibitors, achieved good objective responses in soft tissue and uterine leiomyosarcoma trials [61-63]. Sunitinib was studied in a phase 2 trial conducted by the GOG. Eligible patients were treated with sunitinib 50 mg by mouth daily for 4 weeks, followed by a 2-week break. All participants were pre-treated and had received 1-2 prior lines of chemotherapy. Nine patients (39.1%) had received radiation therapy. Tumor response and progression-free status were assessed every 6 weeks by RECIST. Twenty-five patients enrolled onto the study and 23 were evaluable for efficacy. Participants received a median of one cycle of therapy. Two patients (8.7%) achieved a PR, and 4 patients (17.4%; 90% CI, 6.2-35.5%) were progression-free at 6 months. Median PFS was only 1.5 months, and OS was 15.1 months. Unfortunately, predefined study criteria were not met, and a second stage was not opened for accrual.

mTOR inhibitors

Preclinical studies have identified additional pathways as potential targets in the treatment of leiomyosarcoma [64-67]. A subset of uLMS shows a loss of PTEN, resulting in aberrant

signaling and increased activation of the AKT-mTOR pathway, which leads to unregulated cell proliferation. Gene expression studies have confirmed the upregulation of the PI3K-AKT-mTOR pathway in human uLMS. Targeting the AKT-mTOR pathway may be a promising strategy for the treatment of uLMS. Though primarily studied in preclinical *in vivo* and *in vitro* models, investigators have demonstrated potency of mTOR inhibitors as single agents and in combination with other drugs against uLMS cells. At least one clinical trial, using temsirolimus, demonstrated minimal clinical benefit (stable disease in 3 of 6 patients on trial) of this mTOR inhibitor in patients with all-site advanced LMS [68].

Several preclinical studies demonstrated a response to curcumin and mTOR inhibitors (such as rapamycin) in *in vitro* and *in vivo* models. Curcumin, a naturally occurring substance derived from the plant *Curcuma longa*, has been reported to have cancer-preventative activity. Curcumin disrupts both raptor and rictor in the mTOR pathway. Several authors have shown that curcumin, compared with rapamycin or vector control alone, can reduce uLMS cell and tumor growth in both *in vitro* and *in vivo* models. Similar to rapamycin, data from preclinical studies demonstrated that curcumin also targets the AKT-mTOR pathway and can decrease mTOR phosphorylation, as well as downstream targets, including S6 ribosomal proteins. Unlike rapamycin, curcumin also has the ability to induce apoptosis, suggesting that it may be more potent than rapamycin [66, 67]. Other authors have demonstrated the ability of curcumin to also increase autophagy and activate the ERK1/2 pathway. In preclinical work, when combined with PD 98059, an MEK inhibitor, curcumin could significantly enhance apoptosis and inhibit cell proliferation in SKN uLMS cells [65]. This combination represents an interesting and exciting possibility for patients with uLMS, but will need to be tested in clinical trials. Aurora-A kinase, Aurk-A, has also been shown to be overexpressed in uLMS cells. The combination of rapamycin and MLN8237 (an Aurora-A kinase inhibitor) resulted in synergistic inhibition of cell growth in both *in vitro* and *in vivo* models [64]. Importantly, the most potent effects were observed when MLN8237 was administered before rapamycin. All of this preclinical data represent exciting opportunities for investigators involved in translational research to bring novel therapies to the clinic for patients with uLMS.

Five-year view

We eagerly anticipate the results of the currently accruing randomized phase 3 trial (protocol GOG 0277; NCT 01533207) conducted by the NRG Oncology/GOG collaborative group, which is comparing observation to adjuvant therapy with fixed-dose rate gemcitabine and docetaxel, followed by doxorubicin hydrochloride, in patients with uterine-confined leiomyosarcoma who have undergone hysterectomy +/- BSO. This trial is actively recruiting patients, and investigators estimate the primary completion date will be in 2018. Hopefully, this trial will shed light on whether or not adjuvant therapy in the upfront setting will improve survival in this early-stage, though high-risk, population.

In the current era of developing “personalized medicine”, physicians and scientists are now looking at biologic and targeted therapies in the treatment of many malignancies. Recently published preclinical work investigating the potency of mTOR inhibitors with or without Aurora-K inhibitors represents a new approach to the treatment of uLMS. Clinical trials

investigating the safety and efficacy of these agents in patients with uLMS and soft tissue sarcoma are ongoing. Investigators need to devote future research efforts to better define the molecular pathways involved in the pathogenesis of uLMS. If identified, these pathways could be exploited with targeted therapies that may offer improved survival advantage to our current regimens. A recent publication identified 19 significantly overexpressed genes in uLMS samples compared with normal leiomyoma controls [69]. Sixteen (84%) of the overexpressed genes included cell cycle associated genes (*CDC7*, *CDC20*, *GTSE1*, *CCNA2*, *CCNB1*, and *CCNB2*). These data suggest that cell cycle control may play a key role in the pathogenesis of uLMS, and these agents may be used in the treatment of patients with this disease [69].

Expert commentary

There are few effective treatments for patients diagnosed with unresectable and metastatic uLMS. Even when diagnosed at an early stage, women with uLMS have a high risk of disease recurrence. Most trials investigating the utility of chemotherapy in uLMS have been conducted with patients with advanced or recurrent disease. Ongoing research for the identification of more effective agents in the treatment of uLMS is therefore warranted. In particular, identifying agents that exemplify efficacy in the adjuvant setting by improving survival is imperative. Doxorubicin, either as a single agent or in combination with ifosfamide, and the combination regimen gemcitabine-docetaxel remain the standard first-line cytotoxic regimens for this disease. Although not yet approved in the US, trabectedin may also be an effective alternative. Eribulin mesylate may also represent an exciting alternative agent in the treatment of patients with uLMS, but more studies will need to be done to confirm these findings. The results of ongoing clinical trials are highly anticipated to determine if the administration of adjuvant therapy in the upfront setting provides a survival benefit compared to observation alone. Clinical trials investigating the efficacy of other cytotoxic and targeted agents that exploit specific oncogenic pathways that are activated or overexpressed in uLMS are necessary. Future efforts should focus on better defining the molecular etiology of uLMS in order to make advances in the care of patients with this disease.

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Key issues

- Uterine leiomyosarcoma remains an aggressive disease, with few effective therapies available to alter the natural history of this disease
- Adjuvant therapy has not yet been proven to be effective in this disease
- Single-agent and combination regimens have been studied in phase 2 clinical trials, with modest response
- Doxorubicin and the combination gemcitabine and docetaxel both represent reasonable options as first-line treatment regimens in the adjuvant setting
- Trabectedin, although not approved in the United States, may be effective in the treatment of uterine leiomyosarcoma
- A call to action must be made to identify more effective therapies—cytotoxic or targeted—to alter the natural history of this disease
- Future efforts should focus on better defining the molecular etiology of uterine leiomyosarcoma in order to make advances in the care of patients with this disease

Table 1
Summary of doxorubicin-based trials in adjuvant setting for uterine sarcomas

	# Pts enrolled	Trial population	Trial design	# Patients with recurrent disease (%)	OS (months)	3-year DFS	3-year OS
Doxorubicin vs observation (Omura 1985) [18]	225 (48 uLMS)	Uterine sarcomas	Randomized	All patients: Doxorubicin: 31 (41) Observation: 43 (53) LMS only: Doxorubicin: 11 (44) Observation: 14 (61) 	Doxorubicin: 73.7 Observation: 55.0		
Doxorubicin, cisplatin, ifosfamide + RT vs RT alone (SARCGYN) (Pautier 2013) [28]	81	Uterine sarcomas	Randomized, phase 3	All patients: Arm A: 15 (38.5) Arm B: 26 (62) 		Arm A: 55% Arm B: 41%	Arm A: 81% Arm B: 69%

OS: overall survival, DFS: disease-free survival; RT: radiation therapy; uLMS, uterine leiomyosarcoma

Table 2
Summary of trials investigating the efficacy of gemcitabine-docetaxel in uterine LMS in the adjuvant setting

Adjuvant	# Pts enrolled	Trial population	Trial design	Line of treatment	PFS (months)	OS (months)	2-year PFR (%)	3-year PFR (%)
Fixed-dose rate gemcitabine-docetaxel (Hensley 2009) [24]	25	Uterine LMS	Single-arm, single institution	1 st	13	NR	45% All pts: 59% Stage I/II:	
Gemcitabine- docetaxel + doxorubicin (SARC-005) (Hensley 2013) [27]	47	Uterine LMS	Phase 2	1 st	NR (> 36 months)	NR	78	57

PFS: progression free survival; OS: overall survival; LMS: leiomyosarcoma; PFR: progression-free rate; NR: not reached

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Table 3

Summary of trials investigating gemcitabine-docetaxel in the advanced/recurrent setting

	# Pts enrolled	Trial population	Trial design	Line of treatment	CR N (%)	PR N (%)	ORR N (%)	PFS (months)	OS (months)
Metastatic/advanced/recurrent									
Fixed-dose rate gemcitabine-docetaxel (Hensley 2008) [22]	42	Uterine LMS	Phase 2	1 st	2 (4.8)	13 (31)	15 (35.8)	4.4	16+
Fixed-dose rate gemcitabine-docetaxel (Seddon 2015) [33]	45 (24 uLMS)	All-site LMS	Phase 2	1 st line		11 (25)		7.1	17.9
Fixed-dose rate gemcitabine-docetaxel (Hensley 2002) [25]	34 (29 uLMS)	All site LMS	Phase 2	1 st or 2 nd 	3 (8.8)	15 (44)	18 (53)	5.6	17.9
Fixed-dose rate gemcitabine-docetaxel (Hensley 2008) [23]	51	Uterine LMS	Phase 2	2 nd line	3 (6.3)	10 (20.8)	13 (27)	6.7+	14.7
Gemcitabine vs Gemcitabine-docetaxel (TAXOGEM)* (Pautier 2012) [32]	90 (46 uLMS)	All site LMS	Randomized, Phase 2	2 nd line	Gem: 1 (5)	Gem: 3 (14) Gem-doc = 5 (24)	Gem: 4 (19) Gem-doc % (24)	Gem: 5.5 Gem-doc = 4.7	Gem: 20 Gem-doc = 23
Fixed-dose rate gemcitabine-docetaxel plus bevacizumab or placebo (Hensley 2015) [26]	107	Uterine LMS	Randomized, Phase 3	1 st line			Gem-doc PL: 17 (31.5) Gem-doc Bev: 19 (35.8)	Gem-doc PL: 6.2 Gem-doc Bev: 4.2	Gem-doc PL: 26.9 Gem-doc Bev: 23.3

CR: complete response; PR: partial response; ORR: objective response rate; PFS: progression-free survival; OS: overall survival; LMS: leiomyosarcoma; Gem: gemcitabine arm; Gem-doc: gemcitabine-docetaxel arm.

*Results presented are for patients in the trial with uterine leiomyosarcoma only.