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Uterine sarcomas

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A B S T R A C T

Uterine sarcomas comprise a small percentage of uterine malignancies. The most common uterine sarcoma is leiomyosarcoma (LMS). Early stage uterine LMS is curable with complete hysterectomy with removal of an intact uterus. Patients with metastatic disease may achieve tumor responses with improvements in quality of life, but long-term remissions are rare. In this review article, I outline adjuvant therapies for early stage resected uterine LMS, as well as treatment of metastatic disease.

A R T I C L E I N F O

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INTRODUCTION

Uterine sarcomas comprise less than 10% of uterine malignancies. There are several risk factors associated with uterine sarcomas. These include prior pelvic radiation, tamoxifen use, and certain hereditary conditions, such as hereditary leiomyomatosis and renal cell cancers, and hereditary retinoblastoma.

Uterine sarcoma is either pure sarcoma or mixed sarcoma and carcinoma. Pure sarcomas are further subdivided into leiomyosarcoma (LMS), endometrial stromal sarcoma, or undifferentiated sarcoma. The mixed sarcoma and carcinoma category is comprised of adenosarcoma or carcinosarcoma. Here, I will outline the treatment options for pure sarcomas.

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Local disease

Surgery

Hysterectomy with or without bilateral salpingo-oophorectomy is the surgical treatment of choice in patients who present with suspected uterine sarcoma. In the general population, many women have a diagnosis of uterine leiomyoma (fibroid) and 1 out of 350 of these patients will have a uterine LMS. Unfortunately, there is no definitive diagnostic modality to distinguish between benign leiomyoma and LMS. Therefore, we recommend avoiding uterine morcellation for presumed leiomyoma. The morcellation procedure grinds the uterus and the uterine mass into small pieces to make the surgical procedure and the patient recovery faster. However if LMS is present, this procedure spreads the malignant cells throughout the abdominal cavity resulting in local recurrence and shortened overall survival (OS).[1] The Food and Drug Administration issued a black box warning against power morcellators in 2014. However, these devices are still in use and unfortunately, many patients are not warned of this risk prior to procedure.

Radiation

In one study, 224 patients with stage I and II uterine sarcomas were randomized to radiation vs observation following hysterectomy and bilateral salpingo-oophorectomy. Radiation started 8 weeks after surgery with a dose of 50.40 Gy. Radiation therapy improved local control in uterine carcinosarcoma, however, there was no benefit for 100 LMS patients who received radiation compared to observation.[2] In addition, there was a trend toward worsened survival with radiation. The majority of patients in this study had stage I disease. Postoperative radiotherapy is not effective for stage I (disease confined to the uterus) disease, but some patients with stage II (disease extending beyond the uterus) disease may have local control benefit from radiation, especially those with positive margins.

Chemotherapy

Adjuvant adriamycin given to patients with early stage (I and II) uterine sarcomas in a randomized Phase III trial did not show improvement in progression-free survival (PFS) or OS.[3] However in this trial, the adriamycin dose was lower (60 mg/m^2 for 6 cycles) than standard doses used in other sarcomas (75 mg/m^2). In addition, many subtypes of uterine sarcomas were allowed into this study, including carcinosarcomas and stromal sarcomas, which along with the small 146 patient sample size, makes it difficult to draw definitive conclusions.

A prospective study evaluated the role of 4 cycles of adjuvant fixed-dose-rate gemcitabine and docetaxel in 25 patients with various stages of resected uterine LMS.[4] The authors concluded that the treated patients had prolonged PFS and OS compared to historical controls. This study had several limitations however, including a small number (n = 18) of resected stage I and II disease and a lack of randomization.

In a subsequent Phase II study, 47 patients with resected uterine LMS were treated with 4 cycles of fixed-dose-rate gemcitabine and docetaxel, followed by 4 cycles of low dose adriamycin (60 mg/m^2).[5] The authors were encouraged to find a 2-year PFS of 78% compared to a historical control of 50%. These results led to a randomized Phase III cooperative study comparing adjuvant chemotherapy to observation.[6] Unfortunately, this trial did not meet accrual standards and closed early. Therefore, the benefit of adjuvant chemotherapy for early stage uterine LMS is currently unknown. In current practice, we should consider adjuvant chemotherapy only for resected high-risk stage I and II uterine LMS, including those after morcellation, and stage III disease.

Metastatic disease

Adriamycin/ifosfamide

The standard first-line therapy for uterine LMS is anthracycline-based, most commonly including adriamycin. In a study of 34 metastatic uterine LMS treated with continuous infusion ifosfamide (5 g/m^2) and adriamycin (50 mg/m^2), 10 (30%) patients achieved a remission lasting for an average of 4 months.[7] The combination chemotherapy resulted in 1 death from sepsis and 1 from cardiotoxicity. As single agents, both of these drugs result in response rates around 17%-25%.[8] Some argue that adriamycin dose of 75 mg/m^2 is more effective than a lower dose of 50 mg/m^2. However, a randomized study of adriamycin 50 mg/m^2 vs 75 mg/m^2 (both in combination with ifosfamide (5 g/m^2) failed to show benefit in response rate or OS.[9] Further randomized studies comparing single agent adriamycin to combination adriamycin and ifosfamide in metastatic sarcomas did not show improvement in OS. However, the combination therapy resulted in a higher response rate with more rapid symptom control.[10] In general, combination of adriamycin and ifosfamide should be considered in patients presenting with high volume and symptomatic uterine LMS. Patients who present with asymptomatic low volume disease should receive single-agent adriamycin.

A serious concern with adriamycin is decrease in left ventricular ejection fraction and congestive heart failure. One could consider administering the cardioprotective agent, dexrazoxane, earlier in the course of adriamycin therapy, as 25% of patients will develop systolic dysfunction with doses >450 mg/m^2.[11] The addition of dexrazoxane to adriamycin did not affect the efficacy of chemotherapy in a randomized trial, but it did significantly reduce the risk of systolic dysfunction.[12]

Gemcitabine/docetaxel

Another systemic therapy for uterine LMS is gemcitabine and docetaxel combination. Fixed-dose-rate gemcitabine (900 mg/m^2 over 90 minutes) on days 1 and 8 with docetaxel (100 mg/m^2) on day 8 every 21 days showed efficacy as second-line therapy in metastatic uterine LMS.[13] Patients with prior pelvic radiation received lower doses due to bone marrow toxicity. Thirteen of 48 (27%) patients had objective tumor response with a 9+ month median duration of response. However, the median PFS was only 5.6+ months. A separate trial in the first-line setting showed a higher response rate (36%).[14] The median PFS was 4.4 months and the median response duration was only 6 months in the 15 responding patients.

Single agent gemcitabine is also active in uterine LMS and is a reasonable alternative to combination gemcitabine and docetaxel when there is concern for toxicity. In a small randomized phase II study of advanced soft tissue sarcoma, gemcitabine (900 mg/m^2 over 90 minutes on days 1 and 8) and docetaxel (100 mg/m^2 on day 8) combination was superior to gemcitabine (1200 mg/m^2 over 120 minutes on days 1 and 8).[15] The response rates were low in both groups (16% vs 8%), however, the median OS was prolonged in the combination arm (17.9 mo vs 11.5 mo) stressing the importance of stable disease in sarcoma outcome. In general, patients with metastatic uterine LMS may benefit more from combination gemcitabine and docetaxel compared to single agent gemcitabine if they have reasonable performance status.

Dacarbazine

Dacarbazine also has single agent activity in uterine LMS. In 146 patients with uterine sarcoma, dacarbazine (250 mg/m^2 d1-5) in combination with adriamycin (60 mg/m^2) showed a 24% response rate compared to 16% with single-agent adriamycin.[8] The response rate was higher in uterine LMS compared to other subtypes (25% with adriamycin and 30% with combination), but there was no OS advantage. Temozolomide is an oral prodrug with an active metabolite of

dacarbazine. Oral temozolomide is also an option for uterine LMS with an up to 20% response rate.[16]

Trabectedin

Trabectedin (Yondelis) is approved for patients with unresectable LMS and liposarcoma (LPS). Trabectedin is a synthetic alkylating agent originally derived from the marine organism sea squirt Ecteinascidia turbinate. In a large study, median PFS was longer in patients with LMS or LPS randomized 2:1 to trabectedin vs dacarbazine.[17] Out of 577 patients, 232 had uterine LMS, and the 144 treated with trabectedin had 4 months median PFS compared to 1.5 months in those treated with dacarbazine (n = 88) (HR 0.57, $P = 0.0012$).[18] Response rates were essentially similar in both group (11% with trabectedin vs 9%). However, the clinical benefit rate was 31% with trabectedin vs 18% with dacarbazine. Clinical benefit rate includes stable disease, which is of great clinical value in patients with unresectable sarcoma. A few patients with uterine LMS had a prolonged duration of response with trabectedin. However, toxicity should be taken in to consideration when selecting treatment options. Trabectedin can cause transaminitis, cytopenias, and rhabdomyolysis. In the initial randomized study, 2 of 144 uterine LMS patients died of treatment-related toxicity one due to renal failure and the other of pulmonary distress. In general, one could consider dacarbazine prior to trabectedin in patients with borderline performance status, due to the lack of OS advantage with trabectedin.

Eribulin

Eribulin (Halaven) is a nontaxane microtubule inhibitor approved for previously treated LPS. In a large international study, 228 patients with LPS and LMS treated with eribulin had 2 months (13.5 mo vs 11.5 mo) improvement in median OS compared to 224 patients treated with dacarbazine.[19] Of the 452 patient, 152 LMS patients treated with trabectedin had similar OS compared to 145 dacarbazine treated patients. The uterine LMS subgroup (n = 131) had similar outcomes in both groups. Eribulin was not approved for LMS due to lack of PFS and OS advantage compared to dacarbazine in this subset analysis.

Pazopanib

Pazopanib (Votrient) is a multityrosine kinase vascular endothelial growth factor inhibitor approved for previously treated soft tissue sarcoma except for LPS. Forty-four patients with uterine sarcoma (39 uterine LMS) were among the 343 sarcoma patients treated on 2 pazopanib trials.[20-22] Median duration of response was 3.9 months in uterine LMS patients (range: 1.8 mo-9.4 mo, ORR 11%). In addition, 57% of these patients had stable disease with a median duration of 4.7 months. In general, patients with LMS could have durable responses to pazopanib, however, quality of life should be taken in to consideration since this drug can cause debilitating gastrointestinal toxicity most notably diarrhea. Dose modification must be considered early in treatment to avoid weight loss and worsening of quality of life.

Ipilimumab/nivolumab

Nivolumab is a PD-1 checkpoint inhibitor Food and Drug Administration approved for multiple malignancies. However, in a study of 12 uterine LMS patients, there were no objective responses with a median treatment duration of only 1.8 months.[23]

Ten LMS patients treated with pembrolizumab, another PD1 inhibitor, had no responses but 6 of 10 patients had stable disease.[24] Responses to these checkpoint inhibitors in sarcoma do not seem to correlate with PDL1 tumor expression.

Ipilimumab, a CTLA4 inhibitor, combined with nivolumab showed promising activity in soft tissue sarcoma, especially LMS, with 14% (2/14, 1 uLMS) response rate.[25] In this randomized study, (Alliance A091401) sarcoma patients randomized to combination therapy had 3.5 months (14.2 vs 10.7 months) improvement in median OS compared to nivolumab single agent. We desperately need surrogate markers of response to immunotherapy to better select patients for this treatment modality.[26,27]

Local therapy in metastatic disease

Local therapy is a valid option in certain patients with metastatic uterine sarcomas. Options include cryoablation, microwave ablation, radioembolization, and radiotherapy. These local therapies are appropriate for patients who have growth in a few nodules or multiple lesion in a specific organ. Radioembolization of liver with Yttrium 90 in patients with multiple hepatic metastases show promise in controlling these metastases.[28] In addition, focal radiotherapy or ablation can control metastatic growth in lungs, bone, or soft tissue.

Conclusion

Uterine sarcoma is a curable disease at early stages and treatable when metastatic. The sequence of chemotherapy drugs is not crucial and highly dependent on performance status and volume of disease. Local therapy in the metastatic setting is beneficial in controlling disease and improving quality of life.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.currproblcancer.2019.06.001.

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