

Chemotherapy and uterine sarcomas: a narrative review

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Abstract: Uterine sarcomas are very rare, extremely aggressive, and often associated with poor outcomes. They include different histological variants, Leiomyosarcoma being the most common one and the most represented uterine sarcoma in clinical studies. We have reviewed the medical treatment of uterine sarcomas focusing on the available options for adjuvant therapy and for advanced, metastatic or recurrent disease, including the new targeted therapies that are currently being developed. The role of adjuvant treatment for early-stage diseases is controversial and observation after complete surgical resection remains a valid option. In selected cases at higher risk of recurrence (such as high mitotic index, tumor size >5 cm, previous morcellation) adjuvant chemotherapy can be considered. In advanced diseases, surgery may not be feasible, and systemic chemotherapy may be offered. Anthracyclines ± dacarbazine or ± ifosfamide are recommended as adjuvant or first-line treatment. Gemcitabine and docetaxel combination, trabectedin, ifosfamide, and dacarbazine are possible options for further lines of treatment. The vast majority of low-grade endometrial stromal sarcomas have a very high expression of estrogen and progesterone receptors and hormonal therapy can be the treatment of choice in early-stage as well as in advanced diseases. Recently, novel targeted therapies such as pazopanib, and new immunotherapies such as pembrolizumab, have been investigated in advanced and recurrent diseases. Understanding the biological characteristics of uterine sarcomas and finding predictive biomarkers are critical needs to improve targeted therapies and their impact on survival. Patients have to be well informed about the risks and the potential benefits of the proposed treatments and the inclusion in clinical trials designed for uterine sarcomas should be warranted.

Keywords: Uterine sarcomas; chemotherapy; medical treatment

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Introduction

Uterine sarcomas are very rare and include different histological variants: uterine leiomyosarcoma (uLMS, 63%), endometrial stromal sarcomas (ESS, 21%) subdivided in low-grade ESS (LG-ESS) and high-grade ESS (HG-ESS), high-grade undifferentiated sarcoma (HG-US, 5%) and adenosarcoma (AS, 6%). The rarity of these diseases,

the multiple histological variants, and their prognostic differences make it difficult to perform randomized clinical trials and result in often heterogeneous and difficult patient management (1).

We have reviewed the medical treatment of uterine sarcomas focusing on the available options for adjuvant therapy and for advanced, metastatic or recurrent disease,

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including the new targeted therapies that are currently being developed.

We present the following article following the Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/gpm-20-77>).

Methods

A MEDLINE (PubMed) search of the literature was performed, focusing on papers published in the last two decades. Keywords included “uterine sarcoma”, “uterine leiomyosarcoma”, “chemotherapy and uterine sarcoma”, “adjuvant therapy and uterine sarcoma”. Additional publications were identified via a systematic review of all reference lists within the publications retrieved from the MEDLINE search. In studies including all soft tissue sarcomas, subset analyses specific for uterine sarcomas were extracted.

Discussion

Adjuvant treatment for early-stage diseases

Uterine sarcomas are extremely aggressive and are often associated with poor outcomes, even if diagnosed at an early stage. Relapse rates are reported to be between 53% and 71% after 5 years according to histology and stage (2,3). In 2012, the Memorial Sloan Kettering Cancer Center developed a clinical nomogram that resulted in a more accurate prediction of the 5-year overall survival (OS) than the International Federation of Gynecology and Obstetrics (FIGO) staging systems and American Joint Committee on Cancer (AJCC) classifications. Prognostic factors used are age, tumor size, grade, cervical invasion, mitotic rate, locoregional spread, and distant metastases (4). The stage of disease at the time of diagnosis remains the independent most important prognostic factor. Tumor morcellation during surgery negatively affected prognosis in patients with apparent early-stage uLMS (3).

Chemotherapy

Despite the extremely aggressive behavior of these diseases, the role of adjuvant treatment remains controversial. Several regimens of chemotherapy, radiation, and combination of the two therapies have been investigated over the last years, but the benefit observed was minimal. Moreover, trial data are burdened by several confounding factors such as small sample size and histological heterogeneity. Observation after

complete resection of early-stage diseases remains a valid option. Despite the lack of evidence and the little benefit observed, the increasing use of adjuvant chemotherapy has been observed in recent years (5-7). uLMS are the most represented uterine sarcomas in clinical studies (*Table 1*). There are no specific clinical trials or significant studies regarding the other histological subtypes (HG-ESS, HG-US, and AS).

The single-agent doxorubicin has been used as adjuvant therapy for early-stage diseases for many decades. The first study which attempted to evaluate the efficacy of this agent (60 mg/m² every 3 weeks for a total of 8 cycles) compared to observation failed to demonstrate a statistically significant difference in OS, progression-free survival (PFS), and recurrence rates (8). Ifosfamide (1.5 g/m² for 3 days repeated every 28 days for 3 cycles), another single-agent chemotherapy, was tested as adjuvant treatment: 83% of patients with uLMS had recurrent disease. The small sample size and the heterogeneity of the tumor histologies included in the study did not allow to retrieve reliable results from the analysis of the data (9).

The combination of cytotoxic agents has been studied over the last years to obtain a greater benefit in the adjuvant setting. The combination of gemcitabine-docetaxel, which showed encouraging results in the advanced diseases, was analyzed in a phase 2 trial of women with completely resected, stage I–IV uLMS. The schedule consisted of four cycles of gemcitabine 900 mg/m² a day on day 1 and day 8 and docetaxel 75 mg/m² on day 8. The results were promising: 45% of the patients were disease-free at 2 years with a median PFS of 13 months; 18% of the patients had stage I–II uLMS and had a median PFS of 39 months (10).

More recently, the single-arm SARC 005 study was led to test the combination of gemcitabine and docetaxel followed by doxorubicin in high-grade, uterine confined LMS with no evidence of disease after surgery. Fixed doses of gemcitabine and docetaxel were administered every 21 days for 4 cycles followed by further 4 cycles of doxorubicin 60 mg/m². After a median follow-up of 39.8 months, 78% of patients were disease-free at 2 years and 57% at 3 years. The median time to recurrence was 27.4 months (range, 3–40 months). Even with the limit of the lack of a control arm, this study reached the best results in terms of survival (11). These data encouraged the GOG-0277 trial, designed to compare this regimen with observation, but the study was closed in September 2016 due to insufficient accrual, leaving the question unsolved. In the only 38 patients enrolled, OS did not differ between the

Table 1 Adjuvant chemotherapy in early-stage disease

Authors	Type of study	N	Subtypes	Treatment	Results
Omura <i>et al.</i> (J Clin Oncol 1985)	Randomized, phase 3	156	US (30.7% uLMS)	Doxorubicin 8 cycles vs. observation	No difference in OS, PFS and recurrence rate
Kushner <i>et al.</i> (Gynecol Oncol 2000)	Non-randomized	13	US (46.1% uLMS)	Ifosfamide 3 cycles	83% recurrent disease
Hensley <i>et al.</i> (Gynecol Oncol 2009)	Non-randomized	25	100% uLMS	Gemcitabine-docetaxel 4 cycles	45% disease-free at 2 years; stage I-II PFS 39 months
Hensley <i>et al.</i> (Cancer 2013)	Non-randomized, phase 2	47	100% uLMS	Gemcitabine-docetaxel 4 cycles followed by doxorubicin 4 cycles	78% disease-free at 2 years, 57% at 3 years
Pautier <i>et al.</i> (Ann Oncol 2013)	Randomized, phase 2	81	US (65.5% uLMS; 11% HG-ESS)	Doxorubicin-ifosfamide-cisplatin 4 cycles	PFS improved, but no difference in OS; high toxicities
Hensley <i>et al.</i> (J Clin Oncol 2018)	Randomized, phase 3	38	100% uLMS	Gemcitabine-docetaxel 4 cycles followed by doxorubicin 4 cycles vs. observation	Prematurely closed; no difference in OS

US, uterine sarcoma; uLMS, uterine leiomyosarcoma; HG-ESS, high grade endometrial stromal sarcoma; OS, overall survival; PFS, progression-free survival.

two groups (12).

Similar results had been previously reported by Gadducci *et al.* comparing the impact of adjuvant treatment (chemotherapy and/or radiotherapy) with observation in 126 patients after primary surgical resection of the disease. No difference emerged between patients that received adjuvant treatment and those that were sent to observation (13).

A randomized trial explored the combination of doxorubicin 50 mg/m² on day 1, ifosfamide 3 mg/m² on day 1, and day 2 plus cisplatin 75 mg/m² on day 3 for a total of 4 cycles followed by pelvic irradiation versus radiotherapy alone in 81 patients with completely resected uterine sarcomas. The combined arm showed a DFS at 3 years of 55% *vs.* 41% (P=0.048), but no improvement in OS was observed. However, the combined schedule was associated with remarkably higher toxicities, including two cases of patient death (14).

A retrospective study conducted in two Italian oncologic referral centers analyzed the clinical outcome of anthracycline-based or gemcitabine-based adjuvant chemotherapy in early uLMS. Median DFS was 41.3 months with anthracycline-based regimens compared to 20.9 months with gemcitabine-based regimens (HR: 0.49; 95% CI: 0.30–0.80; P=0.004). Anthracycline-based regimens were independently associated with a better DFS in the multivariable model. OS did not differ between the

two regimens (15).

According to the experience achieved with soft tissue sarcomas, the regimens including adriamycin and dacarbazine for three cycles have been proposed for the treatment of uLMS (1).

According to the international guidelines, due to the lack of proven benefit in early-stage uLMS and the toxicities associated with adjuvant chemotherapies, observation remains an option for patients with completely resected diseases, limiting their exposure to chemotherapy only in case of disease recurrence. In selected cases, with a higher expected risk of recurrence (high mitotic index, tumor size more than 5 cm, morcellation or intraoperative rupture) adjuvant chemotherapy could be considered. In these cases, single-agent doxorubicin or doxorubicin combined with dacarbazine or ifosfamide are recommended. Gemcitabine and docetaxel combination is a further line option (1,6,7).

As for HG-ESS, HG-US, and AS with sarcomatous overgrowth, the standard management after complete resection is observation; however, anthracycline-based adjuvant chemotherapy regimen may be offered in selected cases after multidisciplinary discussion and estimate of the risk-benefit ratio with the patient (1,16). Due to its characteristics, LG-ESS are associated with a favorable prognosis; hence, as observed in a large observational retrospective cohort analysis on patients with HG-ESS and LG-ESS, adjuvant chemotherapy is not associated with

measurable clinical benefits (17).

Hormonal therapy

In uLMS estrogen receptors (ER) and/or progesterone receptors (PR) expression has been reported in 25–80% and 30–70% of the cases respectively. In literature, several case reports are suggesting a potential benefit of aromatase inhibitors (AI), such as letrozole or exemestane, in the adjuvant setting. However, the only randomized phase 2 study which compared letrozole 2.5 mg daily versus observation in completely resected uLMS failed to reach the expected accrual and preliminary data did not show significant differences in PFS (18). The lack of data concerning endocrine therapy in the adjuvant setting does not allow the routine prescription of this treatment.

The vast majority of LG-ESS express ER (87%) and PR (80%) (19). Leath *et al.* in a retrospective study conducted on patients with completely resected LG-ESS and subsequent hormonal therapy (megestrol acetate or medroxyprogesterone) showed a statistically significant prolonged median PFS (94 *vs.* 72 months) (20). According to the guidelines in force, in stage I–II disease, a hormonal adjuvant treatment can be offered: progestins are the most effective agents and hormonal treatment should be continued for at least 2 years. Tamoxifen is contraindicated for its pro-estrogenic effect (1).

Treatment of advanced, metastatic or recurrent disease

At least 30–35% of women who present with disease confined to the uterus or with locoregional spread will develop metastatic disease. The first metastatic site is frequently the lung, while other common locations include the peritoneal cavity, the liver, the skin/soft tissue, the bone, and the brain (21).

When the disease appears to be confined to the abdomen, surgical debulking is often attempted to achieve maximal cytoreduction before adjuvant therapy. Surgical cytoreduction with no gross residual disease improves median PFS and remains an important prognostic factor. Secondary complete cytoreduction may be considered especially in isolated site recurrences; the most studied procedure is pulmonary metastases resection (22).

In some cases, clinicians could offer neoadjuvant chemotherapy (NACT) with or without radiation with palliative intent or in attempt to reduce disease burden before surgical intervention (2).

Chemotherapy

In advanced diseases, surgery may not be feasible, and systemic palliative chemotherapy can be offered to patients with good performance status. As well as in early-stage disease, doxorubicin has been the preferred systemic agent for uLMS in the past decades with a response rate of 16–19%. The combination of doxorubicin with other cytotoxic agents has been tested without significant results (*Table 2*). A large phase 3 randomized trial failed to demonstrate that doxorubicin plus ifosfamide improved OS, only showing a longer median PFS (23). Similar results have been reported by Tap *et al.* in a phase 3 trial on doxorubicin plus evofosfamide versus doxorubicin alone, showing a more unfavorable toxicity profile for the combination (24).

Doxorubicin plus dacarbazine, doxorubicin plus ifosfamide, and doxorubicin alone as first-line therapy for advanced/metastatic leiomyosarcoma were evaluated in a recently published retrospective study conducted on patients treated at European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) sites. Doxorubicin plus dacarbazine showed a significantly longer PFS rather than doxorubicin alone [hazard ratio (HR), 0.72; 95% CI: 0.52–0.99]. OS was better with doxorubicin plus dacarbazine (median 36.8 months) in comparison with both doxorubicin plus ifosfamide (median 21.9 months) and doxorubicin (median 30.3 months) (25).

The combination of gemcitabine and docetaxel was assessed by Hensley *et al.* in a phase 2 trial with interesting results. Even in heavily pretreated patients, the overall response rate was 53% and 47% of the patients were progression-free at 6 months (26). Nevertheless, the randomized phase III trial (GeDDIS) comparing gemcitabine plus docetaxel versus doxorubicin as a single agent in previously untreated advanced unresectable or metastatic soft-tissue sarcomas, including 71 uLMS, did not report differences in PFS and OS. The Authors concluded that doxorubicin should remain the standard first-line treatment for soft-tissue sarcomas (27). Gemcitabine and docetaxel combination could be an option for patients in progression after anthracyclines treatment or for which anthracyclines are contraindicated because of cardiac dysfunction.

Trabectedin was evaluated as a single agent in chemotherapy-naïve patients and compared with other single agents showing a clinically relevant delay in time to progression. In combination with doxorubicin as a first-

Table 2 Trials on the treatment of advanced, metastatic or recurrent disease

Authors	Type of study	N	Subtypes	Treatment	PFS (months)	OS (months)
Judson <i>et al.</i> (Lancet Oncol 2014)	Randomized, phase 3	455	STS (22.3% uLMS)	Doxorubicin-ifosfamide vs. doxorubicin	7.4 vs. 4.6	14.3 vs. 12.8
Tap <i>et al.</i> (Lancet Oncol 2017)	Randomized, phase 3	640	STS (35.9% uLMS)	Doxorubicin-evofosfamide vs. doxorubicin	6.3 vs. 6.0	18.4 vs. 19.0
D'Ambrosio <i>et al.</i> (Cancer 2020)	Retrospective	303	100% uLMS	Doxorubicin-dacarbazine vs. doxorubicin-ifosfamide vs. doxorubicin	9.4 vs. 6.8 vs. 5.4	35.4 vs. 21.4 vs. 29.3
Hensley <i>et al.</i> (J Clin Oncol 2002)	Non-randomized, phase 2	42	100% uLMS	Gemcitabine-docetaxel 4 cycles	4.4	16.1
Seddon <i>et al.</i> (Lancet Oncol 2017)	Randomized, phase 3	257	STS (27% uLMS)	Gemcitabine-docetaxel vs. doxorubicin	23.7 vs. 23.3 weeks	67.3 vs. 76.3 weeks
Hensley <i>et al.</i> (J Clin Oncol 2015)	Randomized, phase 3	107	100% uLMS	Gemcitabine-docetaxel + bevacizumab/placebo	4.2 vs. 6.2	23.3 vs. 26.9
Pautier <i>et al.</i> (Lancet Oncol 2015; update ASCO 2020*)	Non-randomized, phase 2	109	STS (43% uLMS)	Trabectedin-doxorubicin 6 cycles	8.2; 8.3*	20.2; 27.5*
Demetri <i>et al.</i> (J Clin Oncol 2016)	Randomized, phase 3	518	LS and LMS (72.9% uLMS)	Trabectedin vs. dacarbazine	4.2 vs. 1.5	13.4 vs. 12.9
Schöffski <i>et al.</i> (Lancet 2016)	Randomized, phase 3	452	LS and LMS (65.7% uLMS)	Eribulin vs. dacarbazine	–	13.5 vs. 11.5
Van Der Graaf <i>et al.</i> (Lancet 2012)	Randomized, phase 3	369	STS (43% uLMS)	Pazopanib vs. placebo	4.6 vs. 1.6	12.5 vs. 10.7
Mir <i>et al.</i> (Lancet 2016)	Randomized, phase 2	182	STS (30.2% uLMS)	Regorafenib vs. placebo	3.7 vs. 1.8	–
Tap <i>et al.</i> (Lancet 2016)	Randomized, phase 2	133	STS (38.3% uLMS)	Doxorubicin-olaratumab vs. doxorubicin	6.6 vs. 4.1	26.5 vs. 14.7

STS, soft tissue sarcoma; uLMS, uterine leiomyosarcoma; LS, liposarcoma; OS, overall survival; PFS, progression-free survival.

line therapy for locally advanced or metastatic uLMS, Trabectedin was found to yield a disease control rate of 87.2%, with a median PFS of 8.2 months and OS of 20.2 months (28). The data have been confirmed at American Society of Clinical Oncology (ASCO) 2020, where a PFS of 8.3 months and OS of 27.5 months have been presented (29). The combination of drugs gives clinical benefit to patients with advanced-stage uLMS even considering the good toxicity profile. Trabectedin-doxorubicin combination is being compared with doxorubicin alone in an ongoing phase III trial. In metastatic or locally relapsed uLMS trabectedin is reported to be active and well-tolerated (30). After the failure of anthracyclines-based chemotherapy, trabectedin resulted in longer PFS than dacarbazine (4.2 vs. 1.5 months) in a

phase III multicenter clinical trial (31). Given these results, trabectedin is approved for the treatment of advanced or recurrent uLMS after the failure of standard anthracycline-based regimens (6).

Eribulin, a microtubule inhibitor, has shown good results on OS compared with dacarbazine (13.5 vs. 11.5 months), but sub-group analysis showed a greater benefit for liposarcoma rather than LMS (32).

Other agents, including topotecan, cisplatin, paclitaxel, thalidomide, and etoposide, have also been assessed in LMS, however, none has achieved better response rates than the therapies above.

Regarding the other histological variants of uterine sarcoma (HG-ESS, HG-US, and AS) systemic therapies for advanced disease are similar to the ones used in uLMS (1).

Only one prospective phase II study analyzed the role of first-line chemotherapy with ifosfamide (1.5 g/m² given on days 1–5, every 3 weeks) in patients with ESS demonstrating an overall response in 33% of patients (33).

Targeted therapies

Among the targeted therapies approved for the treatment of LMS in progression after previous chemotherapy, pazopanib is a multi-tyrosine-kinase inhibitor that targets signal transduction pathways for cell growth and angiogenesis. The PALETTE study, which enrolled 369 pretreated patients with metastatic soft tissue sarcoma, confirmed a prolongation of PFS (4.6 *vs.* 1.6 months for placebo, $P < 0.0001$) in all patients as well as in the uLMS sub-group (43% of patients). The drug was fairly well tolerated, with only mild fatigue, anemia, stomatitis, and hypertension reported (34).

Regorafenib has been the subject of the randomized phase 2 trial REGOSARC, as maintenance therapy after failure or intolerance to anthracyclines, showing a benefit in terms of PFS (HR 0.45, $P = 0.0046$). A study evaluating regorafenib as maintenance therapy after stabilization or response to doxorubicin in first-line is currently ongoing (35).

The addition of bevacizumab to gemcitabine and docetaxel demonstrated no benefit on OS or PFS but was associated with greater toxicities (36).

Olaratumab is a platelet-derived growth factor receptor (PDGFR) antibody, which combined with doxorubicin showed a significantly longer PFS (6.6 *vs.* 4.1 months, $P = 0.06$) and OS (26.5 *vs.* 14.7 months, $P = 0.0003$) than doxorubicin alone. Several patients reported adverse events of grade 3 or higher in the combination arm, but few discontinued the therapy due to side effects (37). Currently, olaratumab is approved by FDA for the treatment of patients with unresectable soft tissue sarcomas not eligible for surgery or radiation and a phase 3 trial is ongoing.

Checkpoint inhibitors, such as nivolumab and pembrolizumab, have been investigated as therapeutic pathways in uLMS without achieving measurable effects. Although there may be case reports of response to these agents, their use is not warranted outside the clinical trial setting. The use of poly ADP-ribose polymerase inhibitors (PARP-Is) may open new therapeutic perspectives in the near future. A study conducted on 170 patients with LMS demonstrated that the percentage of BRCA mutations is 10% in uterine LMS and only 1% in extrauterine LMS. Furthermore, 13% of uLMS had alterations of gene sequences or loss of other genes (38).

The best synergic effect of PARP-Is seems to be with trabectedin which could induce the activation of PARP1, providing PARP inhibitors the specific substrate (39). The combination of trabectedin and olaparib at active dose levels showed manageable toxicities in a phase 1b study from the Italian Sarcoma Group (40).

Hormonal therapy

According to retrospective data, ER and PR positive tumors seem to be associated with an indolent clinical course. A recent small prospective study analyzed the use of letrozole in patients with ER and/or PR positive metastatic uLMS showing a median PFS of 12 weeks; notably, three patients, all with ER and PR expression >90%, continued to receive letrozole for more than 24 months. AI could be an option in patients with low disease burden and indolent disease (41).

The standard management in ER and PR positive LG-ESS is high-dose progestin therapy (200 mg up to even 1,000 mg/day) since it induces responses or disease stabilizations improving long-term survival. After the failure of the first hormonal line, subsequent hormonal treatments with different agents, such as AI, can be considered and chemotherapy remains an option for hormonal refractory patients or hormone receptor-negative tumors (1).

Neoadjuvant therapy

NACT has been investigated over the years to make conservative surgery more likely, enhance the chance for a complete surgical resection, which is associated with better prognosis, and eradicate the microscopic disease. Despite these theoretical advantages, the use of NACT is limited by several issues, such as the heterogeneity of these tumors and the difficulty in identifying high-grade tumors at preoperative biopsy. Many trials have been conducted including multiple histological types and multiple sites of primary disease; doxorubicin-dacarbazine-mesna-ifosfamide, doxorubicin-ifosfamide, epirubicin-ifosfamide, and doxorubicin-dacarbazine were the most commonly used agents. No exclusive trials for uLMS exist, so specific indications are not available.

Regional hyperthermia is another therapeutic strategy to enhance the NACT effect. Despite promising results, the effects of hyperthermia need to be confirmed by other trials (42).

Conclusions

Uterine sarcomas are rare and extremely aggressive tumors

associated with poor prognosis and high recurrence and mortality rates. Leiomyosarcoma is the most common one and the most represented uterine sarcoma in clinical studies.

The function of adjuvant treatment for early-stage disease is discussed and observation after complete surgical resection remains a valid option. In selected cases at a higher risk of recurrence, adjuvant chemotherapy can be considered, while in advanced diseases medical treatment is the best option. Anthracyclines ± dacarbazine or ± ifosfamide are recommended as adjuvant or first-line treatment. Gemcitabine and docetaxel combination, trabectedin, ifosfamide, and dacarbazine are possible options for further lines of treatment in LG-ESS, hormonal therapy can be the treatment of choice in the early stage as well in advanced diseases. Understanding the biological characteristics of uterine sarcomas and finding predictive biomarkers are critical needs to improve targeted therapies and their impact on survival. Furthermore, specific clinical trials for uterine sarcomas should be designed.

Considering the current knowledge and the lack of conclusive data showing a significant role of chemotherapy neither in adjuvant setting nor for advanced or recurrent disease, a multidisciplinary decision on the therapeutic pathway is mandatory. Patients have to be well informed about the risks and the potential benefits of the proposed treatment and inclusion in clinical trials should be warranted.

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Footnote

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References

1. Ferrandina G, Aristei C, Biondetti PR, et al. Italian consensus conference on management of uterine sarcomas on behalf of S.I.G.O. (Societa' italiana di Ginecologia E Ostetricia). *Eur J Cancer* 2020;139:149-68.
2. Roberts ME, Aynardi JT, Chu CS. Uterine leiomyosarcoma: A review of the literature and update on management options. *Gynecol Oncol* 2018;151:562-72.
3. Juhasz-Böss I, Gabriel L, Bohle RM, et al. Uterine Leiomyosarcoma. *Oncol Res Treat* 2018;41:680-6.
4. Zivanovic O, Jacks LM, Iasonos A, et al. A nomogram to predict postresection 5-year overall survival for patients with uterine leiomyosarcoma, *Cancer* 2012;118:660-9.
5. Friedman CF, Hensley ML. Options for Adjuvant Therapy for Uterine Leiomyosarcoma. *Curr Treat Options Oncol* 2018;19:7.
6. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Uterine Neoplasm, Version 1.2021, October 20, 2020.
7. AIOM (Associazione Italiana di Oncologia Medica). Linee Guida Sarcomi dei tessuti molli e GIST. Edizione 2020.
8. Omura GA, Blessing JA, Major F, et al. A randomized clinical trial of adjuvant adriamycin in uterine sarcomas: a Gynecologic Oncology Group Study. *J Clin Oncol* 1985;3:1240-5.
9. Kushner DM, Webster KD, Belinson JL, et al. Safety and efficacy of adjuvant single-agent ifosfamide in uterine sarcoma. *Gynecol Oncol* 2000;78:221-7.
10. Hensley ML, Ishill N, Soslow R, et al. Adjuvant

- gemcitabine plus docetaxel for completely resected stages I-IV high-grade uterine leiomyosarcoma: Results of a prospective study. *Gynecol Oncol* 2009;112:563-7.
11. Hensley ML, Wathen JK, Maki RG, et al. Adjuvant therapy for high-grade, uterus-limited leiomyosarcoma: results of a phase 2 trial (SARC 005). *Cancer* 2013;119:1555-61.
 12. Hensley ML, Enserro D, Hatcher H, et al. Adjuvant Gemcitabine Plus Docetaxel Followed by Doxorubicin Versus Observation for High-Grade Uterine Leiomyosarcoma: A Phase III NRG Oncology/ Gynecologic Oncology Group Study. *J Clin Oncol* 2018;36:JCO1800454.
 13. Gadducci A, Landoni F, Sartori E, et al. Uterine leiomyosarcoma: analysis of treatment failures and survival. *Gynecol Oncol* 1996;62:25-32.
 14. Pautier P, Floquet A, Gladieff L, et al. A randomized clinical trial of adjuvant chemotherapy with doxorubicin, ifosfamide, and cisplatin followed by radiotherapy versus radiotherapy alone in patients with localized uterine sarcomas (SARCGYN study). A study of the French Sarcoma Group. *Ann Oncol* 2013;24:1099-104.
 15. Fucà G, Fabbroni C, Mancari R, et al. Anthracycline-based and gemcitabine-based chemotherapy in the adjuvant setting for stage I uterine leiomyosarcoma: a retrospective analysis at two reference centers. *Clin Sarcoma Res* 2020;10:17.
 16. Malouf GG, Lhomme C, Duvillard P, et al. Prognostic factors and outcome of undifferentiated endometrial sarcoma treated by multimodal therapy. *Int J Gynaecol Obstet* 2013;122:57-61.
 17. Seagle BL, Shilpi A, Buchanan S, et al. Low-grade and high-grade endometrial stromal sarcoma: A National Cancer Database study. *Gynecol Oncol* 2017;146:254-62.
 18. Slomovitz BM, Taub MC, Huang M, et al. A randomized phase II study of letrozole vs. observation in patients with newly diagnosed uterine leiomyosarcoma (uLMS). *Gynecol Oncol Rep* 2018;27:1-4.
 19. Rizzo A, Pantaleo MA, Saponara M, et al. Current status of the adjuvant therapy in uterine sarcoma: A literature review. *World J Clin Cases* 2019;7:1753-63.
 20. Leath CA, Huh WK, Hyde J Jr, et al. A multi-institutional review of outcomes of endometrial stromal sarcoma. *Gynecol Oncol* 2007;105:630-4.
 21. Bartosch C, Afonso M, Pires-Luís AS, et al. Distant Metastases in Uterine Leiomyosarcomas: The Wide Variety of Body Sites and Time Intervals to Metastatic Relapse. *Int J Gynecol Pathol* 2017;36:31-41.
 22. Cui RR, Wright JD, Hou JY. Uterine leiomyosarcoma: a review of recent advances in molecular biology, clinical management and outcome. *BJOG* 2017;124:1028-37.
 23. Judson I, Verweij J, Gelderblom H, et al. European Organisation and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. *Lancet Oncol* 2014;15:415-23.
 24. Tap WD, Papai Z, Van Tine BA, et al. Doxorubicin plus evofosfamide versus doxorubicin alone in locally advanced, unresectable or metastatic soft-tissue sarcoma (TH CR-406/SARC021): an international, multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2017;18:1089-103.
 25. D'Ambrosio L, Touati N, Blay JY. Doxorubicin plus dacarbazine, doxorubicin plus ifosfamide, or doxorubicin alone as a first-line treatment for advanced leiomyosarcoma: A propensity score matching analysis from the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. *Cancer* 2020;126:2637-47.
 26. Hensley ML, Maki R, Venkatraman E, et al. Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: results of a phase II trial. *J Clin Oncol* 2002;20:2824-31.
 27. Seddon B, Strauss SJ, Whelan J, et al. Gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas (GeDDiS): a randomised controlled phase 3 trial. *Lancet Oncol* 2017;18:1397-410.
 28. Pautier P, Floquet A, Chevreau C, et al., French Sarcoma Group. Trabectedin in combination with doxorubicin for first-line treatment of advanced uterine or soft-tissue leiomyosarcoma (LMS-02): a non-randomised, multicentre, phase 2 trial. *Lancet Oncol* 2015;16:457-64.
 29. Pautier P, Floquet A, Chevreau C, et al. A single-arm multicenter phase II trial of doxorubicin (Doxo) in combination with trabectedin (Trab) given as first-line treatment to patients with metastatic/advanced uterine (U-LMS) and soft tissue leiomyosarcoma (ST-LMS): Final results of the LMS-02 study. *J Clin Oncol* 2020;38:abstr 11506.
 30. Gadducci A, Grosso F, Scambia G, et al. A phase II randomised (calibrated design) study on the activity of the single-agent trabectedin in metastatic or locally relapsed uterine leiomyosarcoma. *Br J Cancer* 2018;119:565-71.
 31. Demetri GD, von Mehren M, Jones RL, et al.

- Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a Phase III randomized multicenter clinical Trial. *J Clin Oncol* 2016;34:786-93.
32. Schöffski P, Chawla S, Maki RG, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. *Lancet* 2016;387:1629-37.
 33. Sutton G, Blessing JA, Park R, et al. Ifosfamide treatment of recurrent or metastatic endometrial stromal sarcomas previously unexposed to chemotherapy: a study of the Gynecologic Oncology Group. *Obstet Gynecol* 1996;87:747-50.
 34. van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2012;379:1879-86.
 35. Mir O, Brodowicz T, Italiano A, et al. Safety and efficacy of regorafenib in patients with advanced soft tissue sarcoma (REGOSARC): a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol* 2016;17:1732-42.
 36. Hensley ML, Miller A, O'Malley DM, et al. Randomized phase III trial of gemcitabine plus docetaxel plus bevacizumab or placebo as first-line treatment for metastatic uterine leiomyosarcoma: an NRG Oncology/ Gynecologic Oncology Group study. *J Clin Oncol* 2015;33:1180-5.
 37. Tap WD, Jones RL, Van Tine BA, D, et al. Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. *Lancet* 2016;388:488-97.
 38. Seligson ND, Kautto EA, Passen EN, et al. BRCA1/2 Functional Loss Defines a Targetable Subset in Leiomyosarcoma. *Oncologist* 2019;24:973-9
 39. Pignochino Y, Capozzi F, D'Ambrosio L, et al. PARP1 expression drives the synergistic antitumor activity of trabectedin and PARP1 inhibitors in sarcoma preclinical models. *Mol Cancer* 2017;16:86.
 40. Grignani G, D'Ambrosio L, Pignochino Y, et al. Trabectedin and olaparib in patients with advanced and non-resectable bone and soft-tissue sarcomas (TOMAS): an open-label, phase 1b study from the Italian Sarcoma Group. *Lancet Oncol* 2018;19:1360-71.
 41. George S, Feng Y, Manola J, et al. Phase 2 trial of aromatase inhibition with letrozole in patients with uterine leiomyosarcomas expressing estrogen and/or progesterone receptors. *Cancer* 2014;120:738-43.
 42. Pasquali S, Gronchi A. Neoadjuvant chemotherapy in soft tissue sarcomas: latest evidence and clinical implications. *Ther Adv Med Oncol* 2017;9:415-29.

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