Podcast 1
Uterine Leiomyosarcoma

What is uterine leiomyosarcoma?

Leiomyosarcoma (LMS) is a rare connective tissue tumour accounting for approximately 16% of all soft tissue sarcomas (STS) and about half of cases are uterine subtype(1). Uterine LMS (uLMS) contributes approximately 1% of all uterine malignancies and is the most common form of uterine sarcoma(2,3).

Most uLMS occur in women over 40 years of age who are usually perimenopausal (3,4). More than half of cases are presented with abnormal uterine bleeding or palpable pelvic mass or enlarged uterus (54%), and nearly one quarter cases reported pelvic pressure or pain (5). Nevertheless, many patients remain asymptomatic (4).

What is the prognosis of uterine leiomyosarcoma?

uLMS is a highly aggressive tumour that is challenging to treat given its resistance to standard therapy, as evidenced by high rates of both recurrence and progression (5). Recurrence rates vary from 45% to 75% with a wide range for sites of recurrence. The most common site of first recurrence is in the lungs, usually within 2 years of primary therapy (5,6).

5-year overall survival (OS) has been reported between 25% and 76% (5). Main prognostic factors are age, tumour stage, and tumour size (4). The tumour's location within the myometrium increases their propensity for early hematogenous spread and dissemination to extra-pelvic sites, being liver, lung, abdominal and bone metastases the most common (2,5).

How is the localised uterine leiomyosarcoma treated?

As with all STS, management of uLMS should be carried out in sarcoma reference centres and surgery remains the standard treatment (7). En bloc total hysterectomy is recommended in localised uLMS (8).

Since symptoms are vague and may mimic to the far other more frequent benign uterine fibroids, a preoperative distinction between the two tumours may be difficult (3,5). Therefore, uLMS is often detected accidentally after removing the uterus or uterine fibroids with or without morcellation (4). Recently, concerns have grown in this regard, as surgeons have utilized uterine morcellation and myomectomy procedures unknowingly in the setting of occult uterine sarcoma (2). Importantly, intraperitoneal morcellation is associated with poorer prognosis (4) and in this line, taking a minimally invasive approach, which is shown to result in better patient outcomes, must be balanced with minimizing the risk of spreading an occult sarcoma within the abdominopelvic cavity (9,10) Therefore, endoscopic supracervical hysterectomy or tumour enucleation and morcellation should be avoided (4).

In general, adjuvant radiotherapy in uterine LMS is not standard, since its value is undetermined, although it can be proposed as an option to the high-risk individual patient (8).

How is the locally advanced/metastatic uterine leiomyosarcoma treated?

In case of local relapse or metastasis the surgical option has to be evaluated regarding a possible complete resection (4). Some particular studies with selected patient populations demonstrate improved OS (45 vs. 31 months) after complete resection of uLMS metastasis (4). Especially resection of single lung or liver metastases may contribute to a prolonged survival (4).

In advanced uLMS, chemotherapy is considered appropriate as it increases survival of women with metastatic leiomyosarcoma (11). As for all LMS, doxorubicin, dacarbazine, trabectedin, gemcitabine alone or in combination with docetaxel, and pazopanib are active agents in ULMS and may be used in a stepwise (7). Choice of treatment for patients with advanced STS, including uLMS, frequently involves finding an appropriate balance between the efficacy and toxicity of available options, aiming to allow patients maintain a normal life. In general, in advanced STS, the higher toxicity of doublet chemotherapy is reasonable to accept when the aim of treatment is to control symptoms or to render a tumor resectable (12).

In general, standard first-line chemotherapy has been largely unchanged for three decades and remains anthracycline-based therapy(6,7,11). A randomized phase III trial of first-line doxorubicin versus doxorubicin and ifosfamide for advanced or metastatic STS showed that doublet chemotherapy significantly prolonged progression-free survival (PFS) with a hazard ratio (HR) of 0.74, but failed to significantly improve OS and was considerably more toxic than doxorubicin alone (11,13).

A phase III study compared doxorubicin with gemcitabine-docetaxel as upfront treatment in advanced STS patients. The combination did not show any improvement in efficacy and was more toxic with some effects on quality of life; therefore, it is not recommended as a first-line therapy for advanced STS, including uLMS (7,14).

A retrospective study of advanced LMS evaluated doxorubicin plus dacarbazine, doxorubicin plus ifosfamide and doxorubicin alone as first line treatment for advance/metastatic LMS. PFS was significantly longer with doxorubicin plus dacarbazine compared with doxorubicin monotherapy (HR = 0.72). Doxorubicin plus dacarbazine was also associated with longer OS, but an adjusted analysis retained an effect for PFS but not for OS (15).

Very recently, a randomized phase III study compared doxorubicin plus trabectedin followed by trabectedin in non-progressive patients vs. doxorubicin monotherapy as first-line therapy of metastatic or unresectable LMS. The combination significantly increased the median PFS compared to doxorubicin alone (12.2 months vs 6.2 months; HR 0.41). The PFS improvement was shown both in the uterine and the soft tissue populations and major clinical benefit in ORR and OS was also observed. Doxorubicin + trabectedin safety profile was as expected, with additional but manageable toxicity (16).

Few chemotherapy agents or combinations have been demonstrated to be active in uLMS that has progressed after standard first line treatment (17). The combination of gemcitabine and docetaxel has been evaluated in different prospective and retrospective studies showing controversial results. In a prospective phase II studies the combination of gemcitabine and docetaxel has demonstrated efficacy as second-line therapy for advanced uLMS associated with a median PFS of 5.6 months, and median OS of 14.7 months (17,18), but at the cost of increased toxicity (40% of discontinuations due to AEs) (19).

However, these efficacy results were not confirmed in a phase II study of metastatic or relapsed LMS from the French Sarcoma Group which showed that gemcitabine plus docetaxel was not superior to gemcitabine alone (median PFS 5.5 vs. 4.7 months) (11,20).

As single agents, retrospective evidence indicated that ifosfamide monotherapy had limited activity in patients with LMS (significantly decreased OS compared with doxorubicin monotherapy; p = 0.0247) (6,7) . Pazopanib is a multi tyrosinkinase inhibitor that may induce disease stabilization in metastatic uLMS and thereby prolong the progression-free interval. Data from a double-blind, placebo-controlled phase III study, including 50% patients with uLMS, showed that pazopanib significantly prolonged PFS in all patients compared with placebo (median PFS: 4.6 versus 1.6 months). However, that longer PFS with pazopanib did not translate into an improvement in OS over placebo (11,21). In addition, clinical experience with pazopanib points to the possibility of rapid tumour growth after treatment discontinuation due to a rebound effect with Vascular endothelial growth factor inhibitors. This key aspect, along with the frequent resistance by patients to receive intravenous therapy after receiving oral therapy, tends to position pazopanib as a treatment choice for later lines (6).

Trabectedin can be considered more than a classical cytotoxic drug given that it also has immunomodulatory and antiangiogenic properties which potentially contribute to a delayed response with a prolonged stabilization (17). It is indicated for the treatment of advanced STS after failure of doxorubicin/ ifosfamide or as front-line treatment in patients unsuited to receive these agents (22). Clinical benefit with trabectedin has been documented in multiple studies performed in patients with STS and uLMS.

In a phase III trial, trabectedin demonstrated significantly improved disease control in leiomyosarcoma and liposarcoma patients who had received prior anthracycline therapy. In the subset of 232 patients with uterine LMS, trabectedin treatment resulted in significantly longer PFS versus dacarbazine (4.0 vs 1.5 months; HR = 0.57), with an acceptable safety profile (23).

In addition, the effectiveness of trabectedin were confirmed in a real-world evidence study in which trabectedin demonstrated to confer clinical benefit in patients with metastatic uLMS after failure to an anthracycline-containing regimen (median PFS and OS: 5.4 and 18.5 months, respectively). Median OS was significantly higher in patients receiving trabectedin in ≤ 2nd line (25.3 months) than in ≥ 3rd line (15.1 months) (24).

Compared to other chemotherapeutic agents used in uLMS, trabectedin has a convenient safety profile, including no cumulative toxicity that allows patients to benefit from a prolonged treatment, with the potential for longer disease control (17). Moreover, clinical evidence showed that PFS can be prolonged when trabectedin treatment is maintained until disease progression (6). Therefore, trabectedin is a suitable choice when the treatment goal is long-lasting tumour stabilization and good patient' quality of life (25).

To conclude, uLMS is a rare tumour that occur in women over 40 years of age who are usually perimenopausal. It is very aggressive with high rates of both recurrence and progression. Standard treatment for local disease is bloc total hysterectomy whereas for advanced uLMS, chemotherapy remains the mainstay of treatment. In general, anthracycline-based therapy remains the standard of first-line treatment. Few chemotherapy agents or combinations have been shown to be active in uLMS

that has progressed to standard first line. Trabectedin with its pleiotropic mechanism of actions represents an important treatment option for advanced uLMS, having demonstrated significantly improved disease control as second-line therapy with an acceptable safety profile.

References

1. Reichardt P. Soft tissue sarcomas, a look into the future: different treatments for different subtypes. Future Oncol. 2014 Jun;10(8 Suppl):s19-27.

2. Ricci S, Stone RL, Fader AN. Uterine leiomyosarcoma: Epidemiology, contemporary treatment strategies and the impact of uterine morcellation. Gynecol Oncol. 2017 Apr;145(1):208–16.

3. D'Angelo E, Prat J. Uterine sarcomas: a review. Gynecol Oncol. 2010 Jan;116(1):131–9.

4. Juhasz-Böss I, Gabriel L, Bohle RM, Horn LC, Solomayer E-F, Breitbach G-P. Uterine Leiomyosarcoma. Oncol Res Treat. 2018;41(11):680–6.

5. Roberts ME, Aynardi JT, Chu CS. Uterine leiomyosarcoma: A review of the literature and update on management options. Gynecol Oncol. 2018 Dec;151(3):562–72.

6. Martín Broto J, Le Cesne A, Reichardt P. The importance of treating by histological subtype in advanced soft tissue sarcoma. Future Oncol. 2017 Jan;13(1s):23–31.

7. Gronchi A, Miah AB, Dei Tos AP, Abecassis N, Bajpai J, Bauer S, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up(☆). Vol. 32, Annals of oncology : official journal of the European Society for Medical Oncology. England; 2021. p. 1348–65.

8. Casali PG, Abecassis N, Aro HT, Bauer S, Biagini R, Bielack S, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol Off J Eur Soc Med Oncol. 2018 Oct;29(Suppl 4):iv268–9.

9. Wong M, De Wilde RL, Isaacson K. Reducing the spread of occult uterine sarcoma at the time of minimally invasive gynecologic surgery. Arch Gynecol Obstet. 2018 Feb;297(2):285–93.

10. Adelman MR. The Morcellation Debate: The History and the Science. Clin Obstet Gynecol. 2015 Dec;58(4):710–7.

11. Seagle B-LL, Sobecki-Rausch J, Strohl AE, Shilpi A, Grace A, Shahabi S. Prognosis and treatment of uterine leiomyosarcoma: A National Cancer Database study. Gynecol Oncol. 2017 Apr;145(1):61–70.

12. Grignani G. Being the ultimate travel companion of a patient with uterine leiomyosarcoma. Manuscript in preparation. 2021;

13. Judson I, Verweij J, Gelderblom H, Hartmann JT, Schöffski P, Blay J-Y, et al. 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 Apr;15(4):415–23.

14. Seddon B, Strauss SJ, Whelan J, Leahy M, Woll PJ, Cowie F, 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 Oct;18(10):1397–410.

15. D'Ambrosio L, Touati N, Blay J-Y, Grignani G, Flippot R, Czarnecka AM, et al. 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 an. Cancer. 2020 Jun;126(11):2637–47.

16. Pautier P. LMS-04 study: A randomised, multicenter, phase III study comparing doxorubicin alone versus doxorubicin with trabectedin followed by trabectedin in n non-progressive patients as first-line therapy, in patients with metastatic or unresectable leiomyosarcom. Ann Oncol. 2021;32(suppl_5):S1283–346.

17. Amant F, Lorusso D, Mustea A, Duffaud F, Pautier P. Management Strategies in Advanced Uterine Leiomyosarcoma: Focus on Trabectedin. Raut CP, editor. Sarcoma. 2015;2015:704124.

18. Hensley ML, Blessing JA, Degeest K, Abulafia O, Rose PG, Homesley HD. Fixed-dose rate gemcitabine plus docetaxel as second-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II study. Gynecol Oncol. 2008 Jun;109(3):323–8.

19. Maki RG, Wathen JK, Patel SR, Priebat DA, Okuno SH, Samuels B, et al. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002 [corrected]. J Clin Oncol Off J Am Soc Clin Oncol. 2007 Jul;25(19):2755–63.

20. Pautier P, Floquet A, Penel N, Piperno-Neumann S, Isambert N, Rey A, et al. Randomized multicenter and stratified phase II study of gemcitabine alone versus gemcitabine and docetaxel in patients with metastatic or relapsed leiomyosarcomas: a Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) French Sarcoma Group Study (TAXOGEM study). Oncologist. 2012;17(9):1213–20.

21. van der Graaf WTA, Blay J-Y, Chawla SP, Kim D-W, Bui-Nguyen B, Casali PG, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet (London, England). 2012 May;379(9829):1879–86.

22. European Medicine Agency. Summary of product characteristics, Yondelis® [Internet]. 2012. Available from: https://www.ema.europa.eu/en/documents/product-information/yondelis-epar-product-information_en.pdf

23. Hensley ML, Patel SR, von Mehren M, Ganjoo K, Jones RL, Staddon A, et al. Efficacy and safety of trabectedin or dacarbazine in patients with advanced uterine leiomyosarcoma after failure of anthracycline-based chemotherapy: Subgroup analysis of a phase 3, randomized clinical trial. Gynecol Oncol. 2017 Sep;146(3):531–7.

24. Rubio MJ, Lecumberri MJ, Varela S, Alarcón J, Ortega ME, Gaba L, et al. Efficacy and safety of trabectedin in metastatic uterine leiomyosarcoma: A retrospective multicenter study of the Spanish ovarian cancer research group (GEICO). Gynecol Oncol Reports. 2020;33:Article 100594.

25. Grignani G, Martín-Broto J, Schuler M, Reichardt P. Trabectedin clinical cases: use according to indication in diverse clinical scenarios. Future Oncol. 2015;11(11 Suppl):15–24.