Systematic Review and Meta-Analysis

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The systemic treatment of uterine leiomyosarcomas

A systematic review. No news is good news?

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Abstract

Background: Uterine leiomyosarcomas are rare malignant mesenchymal tumors. The systemic treatment of these tumors includes chemotherapy and radiotherapy. However, there are still a lot of unanswered questions regarding the ideal therapeutic approach.

Methods: We have conducted a systematic review of the treatment strategies of uterine leiomyosarcomas for the last ten years.

Results: Adjuvant chemotherapy is still a matter of dilemma. Doxorubicin based chemotherapy or the combination of Gemcitabine-Docetaxel are the regimens of choice for the first line setting. Beyond the first line, there are several options;, including chemotherapy, targeted therapy, and recently efforts of introducing immunotherapy to the therapeutic armamentarium of clinicians treating uterine leiomyosarcomas.

Conclusions: Despite the efforts of the clinicians dealing with uterine leiomyosarcomas, the optimal therapeutic algorithm is yet to be described.

Abbreviations: DFS = disease-free survival, EORTC = European Organization of Research and Therapy in Cancer, ESMO = European society of medical oncology, ISGE = International Society of Gynecologic Endoscopy, NCCN = national comprehensive cancer network, OS = overall survival, PFS = progression free survival, PR = partial response, PS = performance status, RT = radiotherapy, SD = stable disease, uLMS = uterine leiomyosarcomas, VEGF = vascular endothelial growth factor.

Keywords: chemotherapy, systemic treatment, targeted therapy, uLMS

1. Background

Uterine leiomyosarcomas (uLMS) are rare mesenchymal malignant tumors of the female genital tract, accounting for 1% to 3% of all uterine malignancies and approximately 30% of uterine sarcomas.[1] uLMSs share complex genetic aberrations, without any specific hallmark molecular and genetic marker.[2] Prognosis is based on tumor staging, according to FIGO staging system, mitotic count, and tumor size. Stage I and II uLMS have a relatively favorable prognosis with a 5-year disease-free survival (DFS) rate of 75.8% and 60.1%, respectively.[3] On the contrary, patients with FIGO stages greater than III tend to recur and metastasize very often. Survival rates for stage III and stage IV uLMS appear with a 5-year DFS of 44.9% and 28.7%, respectively.[3]

The therapeutic strategies of uLMS are described in NCCN (national comprehensive cancer network) and ESMO (European society of medical oncology) recommendations.[4,5] Total hysterectomy is the treatment of choice. Recently, other treatment modalities such as chemotherapy, radiotherapy, and targeted therapies have been used in different settings.[6,7]

En bloc total hysterectomy is the treatment of choice for uLMS, without morcellation or rupture of the tumor intraoperatively.[8] Ovarian preservation should be discussed with premenopausal women who wish to retain hormonal function, especially those with early stages (I and II).[5] Lymphadenectomy does not provide survival benefit and its role in the surgical approach of uLMS is controversial.[9] Importantly, uLMSs tend to metastasize hematogenously and lymph node metastases are uncommon findings.[9]

Radiotherapy (RT) is not recommended in the adjuvant setting.[4,5,10] A randomized phase III clinical trial did not improve overall survival (OS) of patients with stage I and II uLMS and therefore is not recommended.[11] However, there are several

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retrospective studies showing an added value of adjuvant RT on local relapses.[12]

Adjuvant chemotherapy is still a matter of debate.[4,5] A recent randomized phase III clinical trial comparing adjuvant gemcitabine-docetaxel for 4 cycles followed by 4 cycles of doxorubicin with observation was not completed due to lack of accrual.[13] NCCN guidelines for stage I uLMS recommend observation or systemic therapy (category 2B).[5] For stage II and III uLMS, the NCCN panel of experts considers adjuvant chemotherapy as appropriate (category 2B).[5]

Chemotherapeutic regimens showing efficacy against uLMS are doxorubicin, dacarbazine, trabectedin, pazopanib, eribulin, vilnorelbine, and gemcitabine-docetaxel.[14,15] The addition of olaratumab to doxorubicin had initially shown a significant benefit in OS in a phase II study,[16] however, the results of phase III ANNOUNCE clinical trial reported no benefit for both the overall population of the study and the leiomyosarcoma subgroup.[17]

In this context, we aimed to conduct a systematic review of the literature synthesizing all available data regarding the systematic treatment of uLMS.

2. Methods

2.1. Search strategy and data abstraction

This study was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The protocol of this systematic review has been approved by the institutional review board. Eligible articles were identified by a search of the MEDLINE bibliographical database from January 1, 2011, up to December 31, 2019, in an attempt to describe the most recent developments in this field. The search strategy included the following algorithm: uterine leiomyosarcoma AND (neoplasm OR cancer OR sarcoma) AND (guidelines OR consensus OR practice OR recommendation OR trial OR study) AND (chemotherapy OR systemic therapy OR management).

Language restrictions were applied, as only articles in English, French, and German were considered eligible. Two investigators (ML and AK), working independently, searched the literature and extracted data from each eligible study. Reviews, experts' opinion, prospective and retrospective studies were eligible, while case reports were excluded for this systematic review. Manuscripts that did not state the name of the authors were excluded. Additional articles were identified from the reference lists of the retrieved articles ("snowball procedure").

3. Results-Discussion

3.1. Search strategy and selection of studies

Our initial search identified 190 records, 189 of which remained after removing duplicate entries and excluding non-eligible articles from title and abstract screening. After the application of our inclusion criteria by reviewing these potential articles in full-text, 92 articles were included for the qualitative analysis. Sixteen additional articles were also included during the search of the references of all eligible articles and relevant reviews. Overall, 108 articles were eligible for the systematic review. The search strategy and the selection of articles are depicted in Figure 1.

3.2. Characteristics of the eligible studies

We identified 19 reviews and systematic reviews discussing the treatment of uLMS.[6,7,15,18–33] Six guidelines and consensus papers dealing with the optimal approach of uLMS patients were found.[4,5,14,34–36] Retrospective studies including real world data or studies from institutional databases were 18.[37–55]

Adjuvant chemotherapy was studied in 13 reports[56–65] and RT in 2.[12,66] The combination of Gemcitabine-Docetaxel was evaluated in four manuscripts.[13,67–69] An equal number of eligible references referred to Doxorubicin-based regimens.[65,70–72] uLMS patients treated with Pazopanib were discussed in 6 reports.[73–78] Trabectedin efficacy in uLMS was reported in 6 studies.[79–84] Eribulin in uLMS was studied in 3 reports.[85–87] Bevacizumab was reported in 3 references.[88–90] Interestingly, immunotherapy for uLMS was discussed in only 1 report.[91]

According to our findings, less frequently used regimens in the treatment of uLMS included hyperthermic intraperitoneal chemotherapy,[92] palbociclib,[93] alisertib,[80] ixabepilone,[94] letrozlole,[95] paclitaxel-carboplatin,[96] aflibercept,[97] temsirolimus,[98] and curcumin.[99]

3.3. Qualitative synthesis of the eligible studies

uLMS are malignant mesenchymal tumors of the female genital tract. Their prognosis is relatively poor.[41] The therapeutic strategy predominantly includes surgical excision.[50] The role of systematic chemotherapy and RT in the adjuvant setting is not well established.[52] Controversies in the therapeutic approach of these tumors are depicted by the differences found in major guidelines (NCCN[5] and ESMO [4]). Furthermore, the low level of recommendations for several therapeutic choices highlights the need for clinical research.

Surgical excision of the tumor with en bloc total hysterectomy is the treatment of choice, while intraperitoneal morcellation is contraindicated.[56] Recent papers review the laparoscopic and robotic techniques to avoid morcellation, as depicted by the ISGE (International Society of Gynecologic Endoscopy) recommendations.[8] Ovaries preservation is not recommended and should be discussed with the patient. NCCN panel of experts recommend ER/PR testing to guide therapeutic decisions regarding the ovaries.[5] Lymphadenectomy has not been proved to be useful and since uLMS tend to metastasize hematogenously, with lymph node metastases being a rare event, it is not recommended from both NCCN[5] and ESMO[4] guidelines.

3.4. Adjuvant treatment

Adjuvant treatment of uLMS is summarized at Table 1. Adjuvant RT is not recommended. The only prospective trial in stage I and II uLMS did not manage to improve PFS or OS when compared with observation.[11] There are several retrospective studies showing a benefit on local pelvic relapses.[10] Both ESMO and NCCN guidelines conclude that RT is not recommended for stage I uLMS and can be discussed with the patient in cases with higher stages considering special risk factors, such as mitotic count, age and necrosis of the tumor.[4,5]

Adjuvant chemotherapy is a matter of debate.[63] NCCN guidelines in Stage I uLMS recommend either observation or systemic therapy or estrogen blockade in case of ER positive tumors.[5] For stage II and III with completely resected tumors, the panel considers systemic therapy to be appropriate, with or

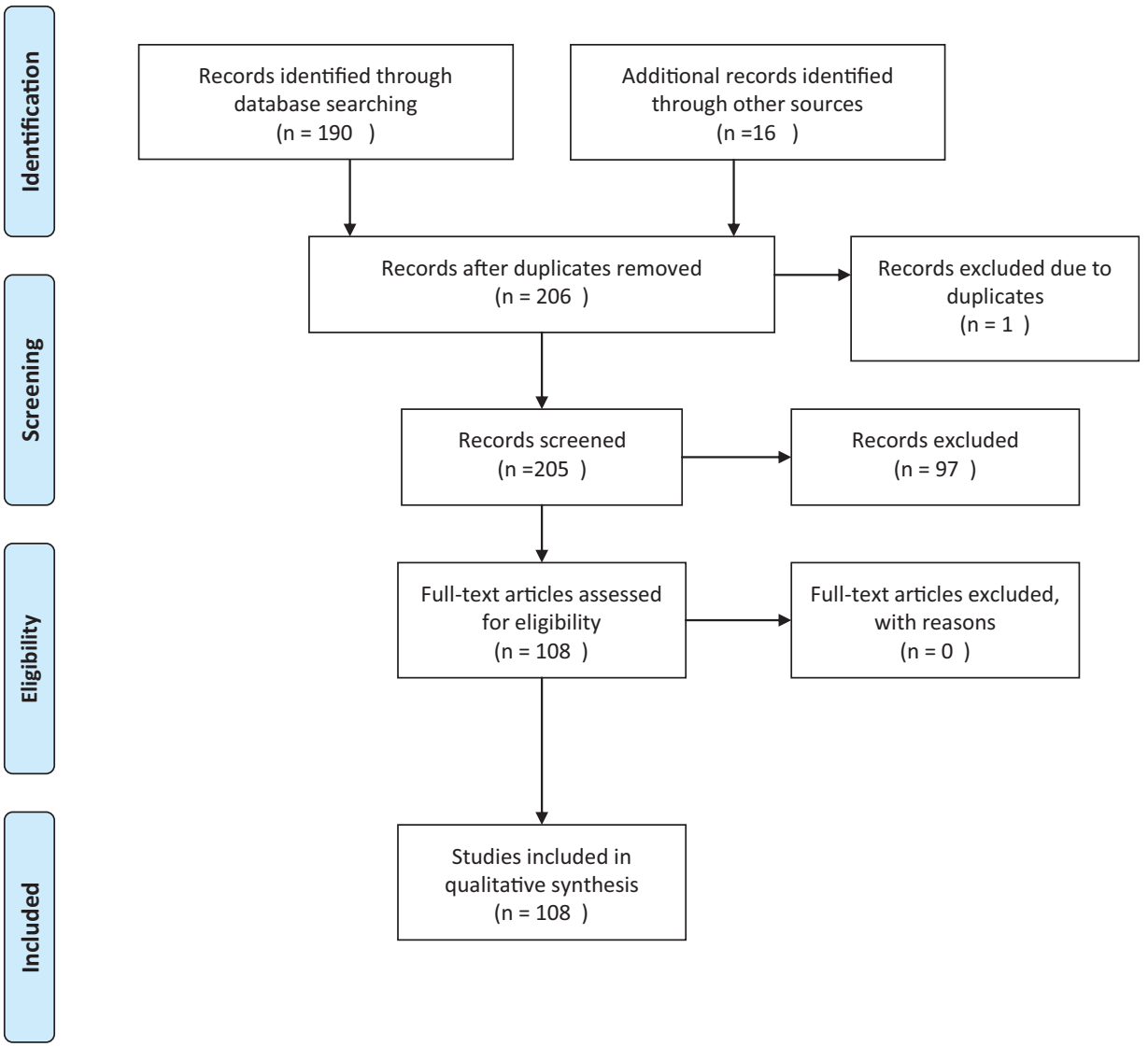

Figure 1. Successive steps during the selection of studies.

without RT.[5] ESMO guidelines highlight the uncertainty of the added value of adjuvant chemotherapy,[4] especially after the early termination due to lack of accrual of the prospective trial comparing 4 cycles of gemcitabine-docetaxel followed by 4 cycles of doxorubicin with observation.[13] In a phase II trial, adjuvant administration of gemcitabine with docetaxel, followed by doxorubicin in women with uterus-limited leiomyosarcoma, resulted in 2- and 3-year PFS rates of 78% and 57%, respectively.[64] In a phase III randomized clinical trial of the French sarcoma group, adjuvant chemotherapy with doxorubicin, ifosfamide and cisplatin followed by RT was compared to RT alone in completely resected uterine sarcomas. The 3-year DFS was increased in the arm of adjuvant chemotherapy (55% for adjuvant chemotherapy vs 41% for RT alone); however the study closed earlier due to lack of accrual.[65] A prospective trial of adjuvant administration of Gemcitabine-Docetaxel showed 2-year PFS rates superior than those published before.[100] In a meta-analysis of adjuvant Gemcitabine-Docetaxel or RT in uLMS, Chae et al[58] did not find any reduction in the recurrence rate of early uLMS patients.

Table 1

Main characteristics of uLMS studies in the adjuvant setting.

Study	Year	Type	Regimen
Reed et al[11]	2008	prospective	RT
Hensley et al[13]	2018	prospective	Gemcitabine-Docetaxel, Doxorubicin
Hensley et al[64]	2013	prospective	Gemcitabine-Docetaxel, Doxorubicin
Pautier et al[64]	2013	prospective	Doxorubicin-Ifosfamide-Cisplatin
Chae et al[58]	2019	Meta-analysis	Chemotherapy, RT
Hensley et al[100]	2009	prospective	Gemcitabine-Docetaxel

3.5. First line treatment

Doxorubicin in combination with Ifosfamide has been tested in a phase II clinical trial of the Gynecologic Oncology Group (GOG) and showed moderate activity in the first line setting of advanced

Table 2

Main characteristics of uLMS studies in the first-line setting.

Study	Year	Type	Regimen
Tap et al[17]	2020	prospective	Doxorubicin-Olaratumab
Pautier et al[69]	2012	prospective	Gemcitabine-Docetaxel
Hensley et al[90]	2015	prospective	Gemcitabine-Docetaxel-Bevacizumab
Sutton et al[101]	1996	prospective	Doxorubicin-Ifosfamide
Tap et al[16]	2016	prospective	Doxorubicin-Olaratumab

or metastatic uLMS.[101] The response rate (RR) found was similar to that in soft tissue sarcomas treated with doxorubicin monotherapy (RR 25%). Olaratumab is a PDGFRa inhibitor, which has been combined with doxorubicin. The addition of this antibody to doxorubicin chemotherapy managed to improve median OS (26.5 vs 14.7 months) for unresectable or metastatic, doxorubicin-naive sarcomas compared to doxorubicin alone. In this phase II clinical trial, 24 of the 66 cases on the olaratumab arm were leiomyosarcomas. In a subgroup analysis, leiomyosarcoma histology, as compared to non-leiomyosarcoma histology, retained the improvement in median OS. However, the phase III clinical study ANNOUNCE, recently reported that the addition of Olaratumab did not offer benefit both to overall population and the leiomyosarcoma group.[16,17]

The combination of Gemcitabine-Docetaxel remains a standard first-line treatment for uLMS.[90] A phase II clinical trial comparing single agent Gemcitabine to Gemcitabine-Docetaxel combination as a second-line therapy in patients with metastatic or relapsed LMS showed similar efficacy for both regimens in uterine and non-uterine LMS.[69]Table 2 highlights the aforementioned trials studying first line chemotherapy in uLMS.

3.6. Systematic and targeted treatments

Several chemotherapeutic regimens have been studied in the systemic treatment of uLMS both with systematic and targeted mechanism of action (Table 3). Addition of anti-VEGF therapy with Bevacizumab to Gemcitabine-Docetaxel, in a randomized phase III study, did not manage to improve PFS, OS, or overall response rate (ORR).[90] Anti-VEGF targeted treatment with Aflibercept, in a phase II clinical trial showed modest activity in patients with uLMS.[97]

A single-arm, phase II trial studying the combination of Gemcitabine and Dacarbazine (DTIC) showed an important clinical efficacy of the regimen with a clinical benefit rate of 57% among LMS patients.[102] The Spanish sarcoma group in a phase II clinical trial evaluated the efficacy of the combination of Gemcitabine with Dacarbazine compared to monotherapy with Dacarbazine. LMS histology was a favorable prognostic factor for prolonged PFS. Among the 16 patients enrolled to the combination arm, 3 showed a response, whereas 2 of the 16 patients showed response to Dacarbazine monotherapy.[103] These data indicate a potentially important activity of DTIC to this histologic entity, which is worth studying in a prospective clinical trial.

Tyrosine kinase inhibitors constitute an effective target for the treatment of sarcomas. In a retrospective analysis of 2 clinical trials (1 phase II and 1 phase III) response to the tyrosine kinase inhibitor pazopanib in patients with uterine sarcomas was similar to those with soft tissue sarcomas (mPFS 3 months for uterine LMS vs 4.5 months for nonuterine LMS). The majority of patients with uterine sarcomas had uLMS and despite heavy pretreatment with more than 2 prior lines of chemotherapy, pazopanib showed a promising signal with median OS (mOS) of 17.5 months compared with 11.1 months for the nonuterine group.[78]

Trabectedin is another effective regimen in the treatment of sarcomas. In a phase II randomized clinical study evaluating the efficacy of trabectedin in uLMS, 2 patients showed partial response (PR) and 10 stable disease (SD).[83] Trabectedin was assessed in combination with doxorubicin as first-line treatment in a phase II trial of soft tissue and uLMS. Out of the 47 patients with uLMS who were enrolled, 28 achieved PR and 13 SD.[82] In a subgroup analysis of a phase III clinical trial enrolling patients with advanced uLMS after failure of anthracycline-based chemotherapy, trabectedin administration resulted in a PFS benefit compared with dacarbazine (4 vs 1.5 months, respectively).[104]

Eribulin is a tubulin inhibitor, which was compared with dacarbazine in a phase III clinical trial. Eribulin improved OS in advanced leiomyosarcomas and liposarcomas. However, histology-driven analysis did not favor eribulin for LMS patients (mOS 12.7 months for eribulin and 13 months for dacarbazine).[87]

Immunotherapy with PD-L1 inhibition in uLMS proved to be ineffective. Nivolumab administration as a monotherapy in uLMS did not show any benefit in a phase II study and, subsequently, further studies regarding this regimen were halted.[91] However, a recent publication has reported a high PDL1 expression and presence of tumor-infiltrating lymphocytes in uLMS, which may imply a possible role for evaluating immunotherapeutic approaches in these tumors.[105] Furthermore, Wilky et al[106] have reported the combination of Pembrolizumab with Axitinib in 4 cases of uLMS with all cases showing disease progression (PD) and 2 soft tissue leiomyosarcomas showing response (1 PR + 1 SD with minor response).

Several other regimens such as paclitaxel-carboplatin,[96] ixabepillone,[94] alisertib,[80] temsirolimus[98] have been studied in uLMS and showed no or limited activity in uLMS.

Aromatase inhibition with letrozole has been studied in a phase II trial accruing patients with unresectable uLMS whose tumors were expressing ER (estrogen receptor)/PR (progesterone receptor). Administration of letrozole was longer to the patients with >90% expression of ER/PR in their tumor cells.[95]

Table 3

Main characteristics of systematic and targeted therapies in uLMS.

Study	Year	Type	Regimen
Hensley et al[90]	2015	prospective	Gemcitabine-Docetaxel-Bevacizumab
Mackay et al[97]	2012	prospective	Aflibercept
Losa et al[102]	2007	prospective	Gemcitabine-Dacarbazine
Garcia Del Muro et al[103]	2012	prospective	Gemcitabine-Dacarbazine
Benson et al[78]	2016	retrospective	Pazopanib
Pautier et al[82]	2015	prospective	Trabectedin
Monk et al[83]	2012	prospective	Trabectedin
Hensley et al[104]	2017	prospective	Trabectedin, Dacarbazine
Schoffski et al[87]	2016	prospective	Eribulin, Dacarbazine
Ben-Ami et al[91]	2017	prospective	Nivolumab
Hyman et al[80]	2017	prospective	Alisertib
Duska et al[94]	2014	prospective	Ixabepilone
George et al[95]	2014	prospective	Letrozole
Okuno et al[98]	2011	prospective	Temsirolimus
Wikly et al[106]	2019	prospective	Pembrolizumab-Axitinib

3.7. Systematic analyses

Systemic chemotherapy of uLMS has been discussed in several reviews. The soft tissue and bone sarcoma group of European Organization of Research and Therapy in Cancer (EORTC) has conducted a systematic review and analysis of all the uterine sarcomas treated with chemotherapy in their database.[21] LMS histology and performance status (PS) were associated with better outcome ($P = .025$ and $P < .001$, respectively).[21] Bogani et al[107] in their systematic review and meta-analysis did not manage to prove the benefit of adjuvant chemotherapy in localized uLMS. Gupta et al,[15] in their systematic review of inoperable, locally advanced, recurrent, or metastatic uLMS have concluded that Gemcitabine-Docetaxel combination has shown longer OS (14.7–17.9 vs 12.1 months) and higher objective response rates (27–53% vs 25%) compared to Doxorubicin monotherapy. In a recent systematic review coping to describe the ideal therapeutic algorithm, the authors concluded that the combination of Gemcitabine with Docetaxel and Doxorubicin with Olaratumab should be the first options for the upfront treatment.[6] However, taking into consideration the lack of benefit from Olaratumab addition to Doxorubicin, it is obvious that the uncertainties regarding the optimal first-line treatment remain. The Taiwan Association of Gynecology in their systematic review of targeted therapies in uLMS concluded that treatment options beyond the second line are limited and research molecules show vague results.[108]

Ongoing and future trials try to answer several important questions regarding the uLMS treatment landscape. The early termination of clinical trials in the field highlights the need for careful study design in the context of orphan diseases and orphan drug development. The ideal regimen for the first-line treatment is yet to be proven. Doxorubicin monotherapy, Doxorubicin-Dacarbazine and Gemcitabine-Dacarbazine combinations are strong candidates for the frontline setting. Several other trials evaluate immunotherapeutic agents alone or in combination with conventional chemotherapy or targeted therapies already used in sarcomas (NCT02997358, NCT04200443, NCT02203760, NCT03463408, NCT03282344).

In conclusion, the systemic treatment of uLMS remains a field with a plethora of unanswered questions. The additive value of adjuvant chemotherapy is still questionable. First-line treatment with Doxorubicin alone or in combination with other agents, as well as the combination of Gemcitabine-Docetaxel, are the main options. In second-line treatment, several regimens can be used with relatively poor results. Translational research with the aim of discovering the vulnerabilities of this tumor type is a matter of unprecedented importance and high priority.

Author contributions

Conceptualization: Anastasios Kyriazoglou, Maria Gavriatopoulou.
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