

Systemic treatment in adult uterine sarcomas

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Abstract

Uterine sarcomas (US) are rare mesenchymal tumours of the uterus and are divided mainly into uterine leiomyosarcoma (uLMS), low grade endometrial stromal sarcoma (LG-ESS), high grade endometrial stromal sarcoma (HG-ESS), adenosarcomas and high grade undifferentiated sarcoma (HGUS). US are often high-grade tumours with a high local recurrence rate and metastatic risk. We here discuss the current standard of care and knowledge of systemic therapy for adult uterine sarcomas, in particular uLMS, LG-ESS, HG-ESS and HGUS, in both the adjuvant as well as the metastatic setting.

Keywords: uterine sarcoma, systemic treatment, chemotherapy, hormone therapy, targeted therapy

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1. Background

Uterine sarcomas are rare. Together, they account for 3-9% of all uterine cancers and the annual incidence is 0.36/100.000 woman-years.(1, 2) Uterine sarcomas (US) are classified into mesenchymal tumours or mixed epithelial and mesenchymal tumours. Mesenchymal tumours are further classified as uterine leiomyosarcoma (uLMS, 63%), endometrial stromal sarcoma (ESS, 21%, usually divided into low grade (LG-ESS) and high grade (HG-ESS)), adenosarcomas (AS, 5%), high grade undifferentiated sarcoma (HGUS, 5%) and other rare subtypes (e.g. alveolar or embryonal

rhabdomyosarcoma).(3, 4) Mixed epithelial and mesenchymal tumours include uterine adenosarcomas and carcinosarcomas.(5-7) Adenosarcomas are mixed tumours with a combination of a benign epithelial component and malignant mesenchymal cells. The risk of relapse is markedly increased in case of sarcomatous overgrowth.(7) Carcinosarcomas, also called malignant mixed Müllerian tumours, are generally regarded of epithelial origin, and therefore are not part of this review. The pathology of uterine sarcomas is known to be difficult. In a population-based study of uterine sarcomas from Norway 168 out of 419 (29%) initially classified US were on review excluded or reclassified as for example leiomyomas or leiomyoma variants according to the WHO criteria.(4) Furthermore, the nomenclature has been changed several times.

The clinical behaviour of the histological subtypes is different. Uterine leiomyosarcomas usually present as a bulky tumour in women > 40 years with complaints of vaginal bleeding (56%), a palpable pelvic mass (54%) and/or pelvic pain (22%).(8) In a significant part of the patients, the diagnosis is set postoperative, instead of the expected leiomyoma(s). Distinction between leiomyoma and leiomyosarcoma is made with conventional morphological criteria (mitosis, atypia and necrosis). The term STUMP (smooth tumours of undefined malignant potential) is used in a setting when both leiomyoma as well as leiomyosarcoma cannot be diagnosed with certainty. Uterine leiomyosarcoma are usually high grade with typically a mitotic rate > 15/10 HPF. The prognosis of leiomyosarcoma is poor, even when confined to the uterus at the time of diagnosis. Recurrence rates are high; between 53-71 %, and the overall five-year survival rate is poor.(8) In a recent Surveillance Epidemiology and End Results (SEER) database reporting of 13,089 US cases between 2000-2012, the five-year relative survival for the group of uLMS patients was 42%.(5) An earlier SEER paper reports a 5-year disease specific survival per stage; stage I–76%, stage II–60%, stage III–45%, and stage IV–29%.(9) In a Norwegian study, the five-year survival rate for uLMS was 51% for FIGO stage I and 25% for FIGO stage II, whereas all patients with stage III-IV died within 5 years.(4)

The term endometrial stromal tumor applies to neoplasms typically composed of cells that resemble endometrial stromal cells of the proliferative endometrium. ESS are predominantly intramural neoplasms exhibiting myometrial invasion and permeation of myometrial lymphovascular spaces. LG-ESS occurs in women between 40-55 years old of whom > 50% is premenopausal. Patients can present with vaginal bleeding, dysmenorrhoea or pelvic pain, but as many as 25% is asymptomatic.(8) Typically, hormone receptors (estrogen, progesterone) are positive on the tumour cells.(8) LG-ESS frequently have JAZF1 rearrangements.(10) Prognosis of LG-ESS is favourable. Recurrences occur in up to one third of the patients and may occur after many years. Five-year survival for stage I-II is 90%, compared to 50% for stage III-IV.(11) High grade ESS present with abdominal bleeding, an enlarged uterus or pelvic mass at a mean age of 50 years (range 28-67). The tumour may appear as intracavitary polypoid or mural masses. The mitotic rate is > 10/ 10 HPF and estrogen and progesterone receptors are negative.(8) Recently, a t(10;17)(q22;p13) translocation has been identified in a large proportion of high-grade ESS. This rearrangement results in an in-frame fusion between YWHAE (exons 1 to 5) and 1 of the 2 highly homologous genes FAM22A and FAM22B (exons 2 to 7), formerly designated as YWHAE-FAM22 and nowadays called YWHAE-NUTM2.(12-14) The presence YWHAE-NUTM2 helps to discriminate HG-ESS from the more common low-grade ESS with JAZF1 rearrangement and from HGUS with no identifiable molecular aberrations, which is important in guiding clinical management.(12, 15) Cyclin D1 can be used as an immunohistochemical diagnostic indicator for HG-ESS with YWHAE-NUTM2 rearrangement.(11) Compared to LG-ESS,

patients with HG-ESS more frequently encounter recurrences and they occur earlier after primary diagnosis. In the SEER database, five-year relative survival for all stage low grade and high grade ESS together was 72.7 %.(5)

Adenosarcomas are characterized by benign epithelial elements and a malignant mesenchymal component. They most commonly present with vaginal bleeding. Pathologic diagnosis is dependent on the identification of the characteristic morphologic features. The most common immunohistochemical markers for adenosarcoma are CD10 and WT1, but these are not specific. High frequency of TP53 abnormalities has been described in high grade AS.(16) The majority of patients present with stage I disease, with a 5-year overall survival of 60 to 80 %. Survival is influenced by the presence of myometrial invasion, sarcomatous overgrowth, lymphovascular invasion, necrosis, and the presence of heterologous elements including rhabdomyoblastic differentiation. The reported prevalence of sarcomatous overgrowth in patients with uterine adenosarcoma varies greatly, from 8% to 65%.(17) Patients with sarcomatous overgrowth have significantly increased risk of recurrence 23 versus 77 % and decreased 5-year overall survival 50 to 60 %.(7) Comparable numbers have been reported in a National Cancer Database study, with a ten years overall survival of approximately 60% in a cohort with 1137 uterine AS patients.(18)

HGUS are very rare and aggressive. They are poorly differentiated sarcomas composed of cells that do not resemble proliferative-phase endometrial stroma. HGUS are separated into uniform and pleomorphic types. Uniform-type HGUS shows permeative myometrial involvement with lymphovascular embolism and no destructive involvement of the myometrium in contrast to pleomorphic undifferentiated ESSs. Uniform-type HGUS shows fusiform spindle cells or round cells. Pleomorphic-type HGUS exhibits high-grade cytological atypia with marked nuclear pleomorphism accompanied in most instances by a high mitotic rate (almost always exceeding 10 MF/10 HPF and sometimes approaching 50 MF/10 HPF) and the presence of tumor necrosis. HGUS is often heterogeneous and composed of different components, e.g. dedifferentiated ESS, dedifferentiated leiomyosarcomas, the sarcomatous component of adenosarcomas or carcinosarcomas with overgrowth of epithelial elements, etc.(15) Approximately 60% of the patients present with stage III or IV disease. The prognosis is very poor with a median survival, once metastasised of less than a year.(8, 19)

We here review the results of systemic treatment in uLMS and ESS in the adjuvant and metastatic settings. The limited available data on AS and HGUS will also be discussed.

2. Adjuvant treatment

As described above, the recurrence rates can be high and disease specific survival may be low in some types of US, especially uLMS. Important risk factors are high mitotic count, tumour spill and morcellation of suspected benign leiomyoma which appear to be leiomyosarcomas by pathology review afterwards. Several attempts have been made to improve disease free survival by adding adjuvant therapy.

2.1 Hormonal therapy

Both uLMS and ESS can express estrogen receptors (ER) and/or progesterone receptors (PR). For uLMS, ER expression has been reported in 18-87% and PR expression in 18-80%. In ESS, ER expression has been shown in 40-100% and PR expression 60-100%.⁽²⁰⁾ HGUS do not express hormone receptors. Adenosarcoma may express both estrogen and progesterone receptors in both the epithelial as well as sarcomatous component, although hormone receptor expression has not been seen in the sarcomatous part of tumours with sarcomatous overgrowth.⁽²¹⁾ Conflicting data have been published about the association between hormone receptor expression and prognosis.⁽²²⁻²⁹⁾

There are no prospective randomized controlled studies of hormonal therapy in uterine sarcomas, neither in the adjuvant nor in the metastatic setting.⁽³⁰⁾ We here summarize the outcome of series of at least ten patients or more.

2.1.1. ESS

In a retrospective series, four out of thirteen ESS patients who received progestins as adjuvant therapy recurred compared with 6 of 9 ESS patients who did not receive adjuvant progestins (31% vs. 67%).⁽³¹⁾ Another retrospective series reports the results of adjuvant hormonal therapy (mainly megestrol acetate or medroxyprogesterone) in thirty low grade ESS patients. The median overall survival with hormonal therapy was 94 months in the patients with adjuvant hormonal therapy versus 72 months in the observation cohort ($p=0.07$).⁽³²⁾ Cheng et al reported a series of 25 low grade ESS who had a median time to progression after adjuvant hormonal therapy of 132 months.⁽³³⁾ In 10 FIGO stage I-II ESS patients treated with adjuvant hormonal therapy (megestrol acetate or aromatase inhibitors), no relapse occurred. Patients were treated between 1977-2007 and the results were reported in 2010, without mentioning the median follow up time.⁽³⁴⁾ In a Chinese retrospective series, 11 out of 114 low grade ESS received some form of adjuvant hormonal therapy. Disease free survival did not differ from patients without or another type of adjuvant treatment and no other details are available.⁽³⁵⁾ Finally, Amant et al reported the results of adjuvant hormonal treatment, defined as a minimum of 200 mg medroxyprogesterone acetate, in 2 out of 22 (9%) and 5 out of 9 (56%) of ESS patients with stages I and III-IV, respectively. Among stage I women receiving adjuvant hormonal treatment or not, 0 out of 2 (0%) and 4 out of 20 (20%) relapsed. And among stages III-IV women receiving adjuvant hormonal treatment or not, 1 out of 5 (20%) and 3 out of 4 (75%) relapsed.⁽³⁶⁾ All together, there is no evidence to support the use of adjuvant hormonal therapy as standard of care in ESS

2.1.2. uLMS

Even less data is available for uLMS and the use of adjuvant hormonal treatment. The results of recently finished randomized phase II study of letrozole versus observation in patients with newly diagnosed uLMS limited to the uterus with at least 10% estrogen receptor expression [NCT00414076] are awaited.

2.1.3. HGUS and adenosarcoma

There is no literature about adjuvant hormonal therapy in HGUS and adenosarcomas. This makes sense since the lack of hormone receptor expression in HGUS. In adenosarcomas, hormone receptor expression has been reported, but we did not find any (adjuvant or palliative) trials or series of ten or more patients treated with hormonal therapy.(21) However, the other way around, adenosarcomas have been associated with tamoxifen use in breast cancer.(37)

2.2 Adjuvant chemotherapy in US

Only a few prospective studies with adjuvant chemotherapy have been performed and these are summarized in table 1.(38-41) The populations of these studies were mixed, including also carcinosarcomas, and had small numbers. These prospective results do not support adjuvant treatment so far. However, it is encouraging that in a single arm phase II study of 47 high grade uLMS patients treated with 4 cycles of gemcitabine-docetaxel followed by 4 cycles of doxorubicin, the median PFS was not yet reached after a median of 39.8 months of follow up.(39)

To date four retrospective series in US have been reported with at least one chemotherapy containing arm. The largest series is an observational cohort study of the National Cancer Database in FIGO stage I ESSS. Out of 2414 women with LG- ESS, 4.8% (n=115) received adjuvant chemotherapy. Approximately one-third (33.4%, 444/1383) of women with HG-ESS received primary adjuvant chemotherapy, and of these women 75.9% (337/444) received multi-agent chemotherapy. Use of adjuvant chemotherapy and radiotherapy were associated with increased survival for HG- ESS, but not in LG-ESS.(42) A second retrospective study in 108 high grade stage I-II uLMS patients comparing adjuvant chemotherapy to radiotherapy or observation did also report no clinical benefit of any adjuvant treatment.(43) The same was the case in a very recent retrospective series of 111 stage I uLMS patients of whom 33 patients received a median of 4 cycles of gemcitabine-docetaxel, without survival benefit.(44) The fourth study by Roque et al presented a retrospective series of 56 uLMS patients treated with chemotherapy (30 gemcitabine-docetaxel, 26 other) compared to radiotherapy (n=41) and observation (n=31). There was no difference in PFS or OS in women with uLMS treated with adjuvant gemcitabine-docetaxel versus those who were observed or received irradiation alone or a chemotherapy regimen other than gemcitabine-docetaxel.(45)

In July 2016, a systematic review and meta analysis was published. Of 360 early stage uLMS patients included, 40% received adjuvant chemotherapy (with or without radiotherapy). These patients were compared to radiotherapy alone or observation (53 and 155 patients). Chemotherapy did not prove to be of benefit in terms of local or distant recurrence rate.(46)

Prospective randomized trials are desperately needed in this disease with high relapse risk. Unfortunately, the Gynaecologic Oncology Group (GOG) 277 phase III trial comparing 4 cycles of gemcitabine-docetaxel followed by 4 cycles of doxorubicin versus observation in high risk uLMS was closed prematurely due to poor accrual [NCT01533207]. One of the important reasons of the difficulty in running this study was the difference between the intensive treatment arm with 8 cycles

of chemotherapy and an observation only arm. Also, for patients just recovering from surgical procedures the prospect of 8 cycles of chemotherapy could be felt quite challenging.

The lack of a universally recognised standard chemotherapy comparator arm, continues to hamper the development of future randomised clinical trials in this setting. Currently the general perception is that there is no routine role for adjuvant therapy, although in practice it may be offered in cases where tumour morcellation took place and other indications with obvious tumour spill during surgical removal of the tumour.

TABLE 1	n	phase	population	% relapse	mDFS (months)	mPFS (months)	mOS (months)	2-year DFS	3-year DFS	5-year DFS
doxorubicin 60 mg/m ² 8 cycles vs. observation(38)	225	III	US* stage I-II	41 vs. 53 (NS)		NR vs. 40.2	73.7 vs. 55.0 (NS)			
gemcitabine 900 mg/m ² d1, d8 +docetaxel 75 mg/m ² d8 q 21 d, 4 cycles. (41)	25	II	uLMS stage I-IV after complete resection			13(median FU >49 months)	NR	45% (stage I-II 59%)		
gemcitabine 900 mg/m ² d1, d8 +docetaxel 75 mg/m ² d8 q21 d 4 cycles followed by +doxorubicin 60 mg/m ² q21d 4 cycles (SARC-005)(39)	47	II	uLMS stage I-IIIa		27.4	NR (median FU> 36 months)	NR	78%	57%	
cyclophosphamide 400mg/m ² d2- vincristine 1mg/m ² d1,d4-doxorubicin 40 mg/m ² d2- dacarbazine 200 mg/m ² d1-4 q28 d 9 cycles(40)	20	II	US* stage I					80%		65%

Table 1. Adjuvant chemotherapy trials in uterine sarcomas.

M; median, DFS; disease free survival, PFS; progression free survival, OS; overall survival, US; uterine sarcomas. *including carcinosarcomas

2.3 Adjuvant radiotherapy alone

Only one prospective trial in early stage (I-II) US is available. Adjuvant radiotherapy was compared to observation and did not result in an improvement of local control, the rate of distant metastases, or OS.(47) Furthermore, a recent report of the SEER database even concluded that (retrospectively) survival was worse in patient treated with surgery and adjuvant radiotherapy compared to surgery alone.(5) Therefore, there is no routine role for radiotherapy in this setting.

2.4 Combined radiotherapy and chemotherapy

In the SARCGYN trial, 81 patients with FIGO stage \leq III US (11% HGUS, including carcinosarcomas) were treated with four cycles of doxorubicin 50 mg/m² d1, ifosfamide 3 g/m², d1-2, cisplatin 75mg/m² d3, (API) and G-CSF q 21 days followed by radiotherapy compared to radiotherapy alone. This study was closed prematurely because of poor accrual. The 3-year disease free survival rates were 55 vs. 41% (p=0.048), respectively, but without improvement of the 3-year OS (81vs 69%, p=0.41), respectively. Toxicity was high with grade 3-4 toxicity (mainly bone marrow suppression) in up to 76% of patients and two toxic deaths due to febrile neutropenia.

2.5 Conclusion - adjuvant setting

Currently, there is neither prospective, nor retrospective, evidence in favour of adjuvant treatment for uterine sarcomas. However, expert opinions mention the possibility to consider adjuvant therapy in selected cases with high risk US. On individual base, for hormone receptor positive HG-ESS hormonal therapy might be considered, carefully balancing the unproven efficacy versus the possible negative effects. Because of its good prognosis, adjuvant hormonal therapy in LG-ESS is not clinically meaningful. For uLMS, adjuvant chemotherapy (e.g. 4-6 cycles of doxorubicin or gemcitabine-docetaxel) might be considered in younger and otherwise healthy patients with a high risk on recurrence (e.g. high grade, tumour spillage or morcellation), after discussion in a multidisciplinary sarcoma tumour board. For HGUS, unfortunately, no conclusion can be made with the unfortunate premature closure of the phase III study.

3. Metastatic treatment

3.1 Hormonal therapy

3.1.1. ESS

Again, only case reports and small retrospective series are available. We here discuss series of at least 10 patients. The Royal Marsden Hospital single experience observed objective response in 46.2% and clinical benefit in 92.4% in 13 metastatic ESS patients treated with first line hormonal therapy. Aromatase inhibitors were prescribed as first endocrine line in 11 out of 13 patients and progestins in the remainder, while in second line treatment other aromatase inhibitors were prescribed in 7 out of 10 patients, followed by progestins and GnRH analogues. Median PFS for first line was 4.0 years, with a 5-year PFS rate of 30.8%. Median PFS for second line hormonal treatment was 3.0 years, with a 2-year PFS rate of 88.9% (95% CI: 68.3 - 100.0).⁽⁴⁸⁾ A Dutch series of 11 LG-ESS patients with residual or recurrent disease treated with megestrol acetate or aromatase inhibitors, observed in 9 (82%) patients an objective response (4 complete responses; 5 partial responses). The response duration ranged from 4 to 252 months (median 48 months).⁽⁴⁹⁾ Ioffe *et al.* reported stable disease, complete or partial response in 14 of 18 ESS patients with recurrent or progressive disease who were treated with hormonal therapy (range of follow up: 6–124 months).⁽²⁹⁾

In second line, only case reports are available.^(50, 51)

Importantly, all case series are small and retrospective, and the natural behaviour of ESS can be indolent.

3.1.2. uLMS

Only one prospective phase II trial with letrozole has been performed in 27 ER and/or PR positive uLMS patients with a median of 2 prior lines of systemic therapy. The median PFS was 12 weeks. The best response was stable disease in 14 patients (54%). Three patients, all with tumours expressing ER and PR in > 90% of tumour cells, continued to receive letrozole for > 24 weeks. Median duration of therapy for the study population was 10 weeks. The most common reason for treatment discontinuation was disease progression (85%).⁽⁵²⁾ In a retrospective series with sixteen patients with measurable advanced uLMS, patients were treated with an aromatase inhibitor (first line mainly letrozole, second line mainly exemestane). Median PFS in first line was 14 months, and prolonged PFS was more likely to be observed in patients with low grade compared to high grade ULMS (20 months vs. 11 months), and in moderate strong ER positive compared to weak ER positive ULMS (20 months vs. 12 months). Best response was a partial response in 2 out of 16 patients (12.5%) and the clinical benefit rate, defined as complete response plus partial response plus stable disease ≥ 6 months, was observed in 10 out of 16 patients (62.5%). Median duration of second line was 3 months and median PFS was not reached. The 1-year PFS rate for the second line aromatase inhibitor was 80%.⁽⁵³⁾ The Memorial Sloan-Kettering Cancer Centre presented their experience in 34 advanced or recurrent uLMS patients (65% ER+, 29% PR+) treated with aromatase inhibitors. Median PFS was 2.9 months and best objective response was partial response in 3 out of 34 patients (9%) (all of whom were ER positive). In the subgroup with ER or PR positive uLMS, the 1 year progression free survival rate was 28%.⁽⁵⁴⁾

3.1.3. Conclusion hormonal therapy- metastatic setting

Although prospective evidence is scarce, the series presented do show that in selected cases (e.g. ER and/or PR positive, low grade, low volume disease) hormonal therapy can be attractive in stabilising disease and ultimately postponing chemotherapy. This is more the case in ESS than in uLMS. In the majority of patients, hormonal therapy has the advantage of being well tolerated and less toxic than systemic chemotherapy. However, almost all presented data are retrospective. A selection and publication bias must be considered and there is a lack of systematic analysis of the hormone receptor status. The lack of available data of control patients makes it difficult to interpret the results of the observations as discussed. Objective radiological response is the most convincing indication of efficacy of treatment in these uncontrolled studies and case series.

3.2. Chemotherapy in US

Despite many efforts, the 5-years disease specific survival for all types of locally advanced and metastatic US (including carcinosarcomas) did not improve in the past decennium.(5, 9) Multiple prospective trials with palliative chemotherapy have been done (Table 2). They encompass the whole range, from smaller studies in uLMS only to larger soft tissue sarcoma (STS) trials including also uterine sarcoma or leiomyosarcoma patients of non-uterine origin. Due to its rarity and its more indolent behaviour, only small numbers of ESS and HGUS patients have been included in STS trials. Furthermore, one must consider that part of the prospective trials and all of the retrospective series have been done without central pathology review and that up to 30% of the pathological diagnosis may be wrong.(4)

The National Cancer Database of the United States concluded that chemotherapy adds 8.5 months benefit compared to untreated patients with metastatic uLMS (19.4 vs. 10.9 months) in an observational cohort study of patients diagnosed between 1998-2013.(42) Recently, a pooled analysis of 269 metastasised US patients treated within 13 trials (total 3270 STS patients) of the EORTC Soft Tissue and bone Sarcoma has been published.(55) Median OS was 10.4 months, median PFS 4.1 months. Four categories of chemotherapy were evaluated; anthracyclines alone, ifosfamide alone, combined doxorubicin-ifosfamide and the combination of cyclophosphamide, doxorubicin, vincristine and dacarbazine (CYVADIC). Clinical outcome was not influenced by category of chemotherapy. Histological subtypes were grouped as LMS versus others. Lower response rates were observed in LMS (19 versus other 33%) and the response for ifosfamide as single agent was only 5% for al US. Gemcitabine-docetaxel was not part of this analysis.

In table 2 we summarize the prospective trials with palliative chemotherapy in US or STS trials important for the nowadays insights in the standard of care for STS in general including US. Where available, numbers of (u)LMS within general STS trials have been provided. The majority of the studies had negative results and did not improve the survival of patients with advanced or metastatic uterine sarcomas. We here discuss the prospective trials summarized in table 2.

TABLE 2	popula tion	Line of treat	P h as	n ((u)LM S)	RR (%)	3mo PFS (%)	6mo PFS (%)	PFS (m ont	OS (months)	Year of public ation
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		ment	e					hs)		
First line										
gemcitabine-docetaxel (56)	uLMS	1	II	44	25	70.5	59.1	7.1	17.9	2015
doxorubicin vs. gemcitabine-docetaxel(57)	STS	1	III	257(71 uLMS, 47 LMS)	-	-	-	23.3 vs. 23.7 weeks	76.3 vs. 67.3 weeks	2017
gemcitabine-docetaxel vs. gem-doc-bevacizumab(58)	uLMS	1	III	107	31.5 vs. 35.8	-	-	6.2 vs. 4.2	26.9 vs. 23.3	2015
gemcitabine-docetaxel (59)	uLMS	1	II	42	35.7	-	19	4.4	16+	2008
liposomal doxorubicin(60)	uLMS	1	II	35	16	Median response duration 4.1 months.				2005
doxorubicin- ifosfamide(61)	uLMS	1	II	34	30.3	Median response duration 4 months.				1996*
Doxorubicin vs. doxorubicin- ifosfamide(62)	STS	1	III	454 (113 LMS)	14 vs. 26	-	-	4.6 vs. 7.4	12.8 vs.14.3	2014
doxorubicin vs. doxorubicin+ cyclophosphamide(63)	US	1	III	104 (38 uLMS, 11 ESS)	19 vs. 19			5.1 vs. 4.9	11.6 vs. 10.9	1985
doxorubicin- palifosfamide vs. doxorubicin(64)	STS	1	III	447 (138 LMS)	28.3 vs. 19.9			6.0 vs. 5.2	15.9 vs. 16.9	2016
doxorubicin- evofosfamide(65)	STS	1	II	91(28 LMS)	36	-	58	6.5	21.5	2014
doxorubicin +/- olaratumab(66)	STS	1	Ib -II	15 (Ib) + 133 (II), of who 51	18 vs 12	-	-	6.6 vs. 4.1	26.5 vs. 14.7 (HR 0.47 LMS, 0.56 other)	2016

				LMS						
doxorubicin-dacarbazine +/- ifosfamide(67)	STS	1	III	340 (59 LMS)	17 vs. 32	-	-	4 vs. 6	12 vs. 13	1993
trabectedin-doxorubicin(68)	uLMS or LMS	1	II	108 (47 uLMS)	60 uLMS	87 uLMS	72 uLMS	8.2 uLMS	20.2 (median FU 9.9 mo)	2015
hydroxyurea-dacarbazine-etoposide(69)	uLMS	1	II	38	18.4	-	-	-	15.0	1996
cisplatin(70)	US	1	II	96:33 uLMS 63 MMT	3 uLMS 18 MMT				7.0	1991
topotecan(71)	uLMS	1	II	36	11	Median duration of response 3.3 months.			2000	
dacarbazine-mitomycin-doxorubicin-cisplatin-sargramostim(72)	uLMS	1	II	18	27.8	-	-	5.9	14.2	2005
mitomycin-doxorubicin-cisplatin(73)	uLMS	1	II	37	23	-	-	-	6.3	2002
etoposide(74)	uLMS	1	II	28	0	-	-	2.1	9.2+	1996
First or second line										
gemcitabine-docetaxel(75)	LMS	1 or 2	II	34(85%)	52.9	64.7	47	5.6	17.9	2002
High dose ifosfamide 12 gr/m ² in 3 days every 28 days(76)	STS	1 or 2	II	124 (33)	16% (LMS 5%)	-	-	15 weeks	-	2000
Paclitaxel-carboplatin(77)	US	1 or 2	II	13	15.4	-	-	2.2	12.4	2012
trimetrexate(78)	uLMS	1 or 2	II	23	4.3	-	-	2.2	7.2+	2002
Second line										
gemcitabine-docetaxel (79)	uLMS	2	II	51	27	73	52	5.6 +	-	2008

gemcitabine-docetaxel(80)	uLMS cohort	2	II	21	23.8	71.4	47.6	4.7	23	2008
gemcitabine(81)	uLMS	2	II	42	20.5	-	-	4.9	-	2004
ixabepilone(82)	uLMS	2	II	26	0	-	-	1.4	7.0	2014
etoposide(83)	uLMS	2	II	29	6.9	-	-	2.1	7.6+	1998
Beyond second line										
gemcitabine-darabazine vs. dacarbazine(84)	STS	≥2	II	109 (32 LMS)	12 vs. 4	56 vs. 37	-	4.2 vs. 2 (LMS 4.9)	16.8 vs 8.2 (LMS 18.3)	2011
trabectedin vs dacarbazine(85)	LMS or lipo	≥3	III	518 (40% uLMS)	9.9 vs 6.9	-	-	4.2 vs. 1.5	12.4 vs. 12.9, HR 0.58 in uLMS subgroup	2016
eribulin vs dacarbazine(86)	LMS or lipo	≥3	III	452 (297 LMS of who 131 uLMS)	4-5	33 vs 29	-	2.6 vs 2.6	13.5 vs. 11.5 (benefit mostly for lipo)	2016
All lines										
Gemcitabine-docetaxel(87)	STS	All	IV	228(57 LMS)	16% (LMS 26.3 %)			3.3	10.3	2017
gemcitabine-docetaxel(88)	uLMS	All	-	9	33	-	-	-	-	2014
doxorubicin vs. doxorubicin+ dacarbazine(89)	US	All	III	226 (72 uLMS, 15 ESS, 17 HGUS)	16 vs. 24	-	-	3.5 vs. 5.5	7.7 vs. 7.3	1983
mitoxantrone(90)	US	All	II	29 (12 uLMS 17 MMT)	0	-	-	1.4	4.1	1990

Table 2. Chemotherapy trials in advanced or metastatic uterine sarcomas.

M; median, mo; months, RR; response rate, PFS; progression free survival, OS; overall survival, US; uterine sarcomas, uLMS; uterine leiomyosarcoma, LMS; leiomyosarcoma, lipo; liposarcoma, ESS endometrial stromal sarcoma, HGUS; high grade uterine sarcoma, MMT; mixed Müllerian tumour, STS; soft tissue sarcoma

3.2.1. Efficacy of chemotherapy in first line

As in other soft tissue sarcomas, doxorubicin is still the first line treatment in uterine sarcomas. Mainly all first line trials in US or (u)LMS were doxorubicin based or used gemcitabine-docetaxel.(56, 58, 72, 73, 75, 79, 80) For a long time, it was debated whether single agent doxorubicin or the combination of gemcitabine-docetaxel was best in (u)LMS. Recently, the results of the UK GeDDiS Phase III trial have been published. This trial included 257 patients with STS who were randomized between doxorubicin 75 mg/m² q 21 days or the combination of gemcitabine 650 mg/m² Day 1 and 8, q21 days and docetaxel 75 mg/m² every 21 days. No significant difference in median PFS (23.3 and 23.7 weeks) or median OS (76.3 vs. 76.3 weeks) for doxorubicin versus gemcitabine-docetaxel were reported and response rates of 20 and 19% for both treatment arms. Further subgroup analyses were done comparing leiomyosarcoma versus other sarcomas (p=0.14), and uterine leiomyosarcoma versus other sarcomas (p=0.38), but again no differential effect was evident between the two treatment groups.(57) The authors concluded that single agent doxorubicin is still the preferred first line treatment in STS and the results in the (u)LMS cohort do not support other preferences. The addition of olaratumab to doxorubicin showed an impressive improvement of OS compared to doxorubicin alone in the Phase Ib-II trial (26.5 vs. 14.7 months) in unselected STS but needs confirmation in a Phase III trial, which has recently completed accrual and results are expected around 2019-2020.(66) [NCT02451943] In those STS patients in need for a volume response (e.g. induction therapy or because of palliative reasons) the combination of doxorubicin and ifosfamide is recommended.(62) However, the European Society of Medical Oncology (ESMO) guidelines suggests the combination of doxorubicin-dacarbazine (67, 89) instead of doxorubicin combined with ifosfamide in case combination therapy is warranted, since the activity of ifosfamide is limited in uterine leiomyosarcomas.(55, 67, 91) Anthracycline based combination therapy in first line palliative treatment is considered to be more toxic and should be reserved for patients in need for a volume response, e.g. in case of severe symptoms.

Based on an encouraging objective response rate of 60% in the uLMS subgroup treated with the combination of doxorubicin and trabectedin in a non-randomised phase II trial(68), a phase III trial; combining doxorubicin plus trabectedin versus doxorubicin followed by trabectedin in uterine or soft tissue leiomyosarcoma patients is currently in preparation. [NCT02997358] Recently, a randomised phase II study of Martin-Broto *et al.* with the same combination in STS patients versus doxorubicin was closed because of futility after interim analysis.(92)

3.2.2. Efficacy of chemotherapy after failure of the first line

Multiple trials have been performed in second line and further. The results are summarized in table 2. Proportions of (u)LMS patients in US or STS trials have been mentioned but should be interpreted with caution since these trials were not powered for subgroup analyses. The results do not warrant a different approach for uterine sarcomas as for STS in general, although details may be slightly different. Again, ifosfamide is less frequently used in (u)LMS both in first as well as in second line.(55)

Trabectedin (68, 85) and dacarbazine(84, 86) are the most frequently used drugs. A direct comparison has been made in a phase III trial with trabectedin vs. dacarbazine in patients with leiomyosarcomas and liposarcomas in third line and further.(85) A total of 518 patients were enrolled and randomly assigned to either trabectedin (n = 345) or dacarbazine (n = 173). Median PFS for trabectedin vs. dacarbazine was 4.2 vs. 1.5 months; hazard ratio, 0.55; P < 0.001). In the pre-defined sub-analyses all subgroups benefited from trabectedin, although the benefit was not statistically significant in all these subgroups. The interim analysis of OS (64% censored) demonstrated a non-significant 13% reduction in risk of death in the trabectedin arm compared with dacarbazine (median OS for trabectedin v dacarbazine, 12.4 v 12.9 months; hazard ratio, 0.87; P = 0.37). In a post hoc subset analysis of the uLMS cohort of this trial, trabectedin treatment resulted in significantly longer PFS versus dacarbazine (4.0 vs. 1.5 months), without difference in OS (14.4 vs. 12.9 months). Objective response rate was 11% with trabectedin vs. 9% with dacarbazine (P=0.82) and clinical benefit rate for trabectedin was 31% vs. 18% with dacarbazine (P=0.05).(93)

Despite the negative results for leiomyosarcoma in the recently published phase III eribulin trial, the results of the comparator dacarbazine arm are interesting.(86) A total of 452 patients with intermediate-grade or high-grade advanced liposarcoma or leiomyosarcoma (28-30% uLMS) who had received at least two previous systemic regimens for advanced disease (including an anthracycline) were 1:1 randomized to eribulin mesilate or dacarbazine (850 to 1200 mg/m² intravenously on Day 1) every 21 days until disease progression. OS was significantly improved in patients assigned to eribulin compared with those assigned to dacarbazine (median OS 13.5 vs. 11.5 months; hazard ratio 0.77). This OS benefit was only seen in liposarcoma patients (median OS 15.6 months vs. 8.4 months, respectively) and not in those with leiomyosarcoma (12.7 vs. 13.0 months). Median PFS was similar in both treatment groups: 2.6 months. Remarkably, this trial confirms the activity of dacarbazine in leiomyosarcoma by its relatively long survival of LMS patients who were included in a third line or higher trial. Temozolomide, the prodrug of dacarbazine, had been reported to induce some (partly prolonged) responses in a retrospective series of in total 19 patients.(94)

Due to its rarity, the data on chemotherapy in metastatic ESS are sparse. For both ESS and HGUS, no specific conclusions can be withdrawn because of a lack of evidence.

3.2.3. Conclusion chemotherapy– metastatic setting

Most trials focused on STS or (u)LMS, and rarely include patients with ESS or HGUS. By evidence and efficacy, first line treatment of choice still remains doxorubicin (+/- olaratumab if available) or perhaps doxorubicin-dacarbazine in case of the need of combination therapy. Within the next few years, the results of the ongoing phase III trials may (or may not) change this into doxorubicin-olaratumab or maybe doxorubicin-trabectedin. After first line therapy, many drugs have some activity but in general the prognosis remains poor. Choice of treatment in this setting includes consideration of toxicity profile and patient preference. Trabectedin, dacarbazine and gemcitabine based chemotherapy are active options. Clinical trial options should always be considered.

3.3. Other, non cytotoxic, systemic therapy in second line and further

Many cancer patients benefit from the big breakthroughs of the past few years, such as immunotherapy and targeted therapy. Unfortunately, this is not the case for uterine sarcomas.

3.3.1. Immunotherapy

Only a limited number of studies have been performed to assess efficacy in uterine sarcomas (Table 3). Uterine LMS exhibit moderate immunohistochemical expression of PD1 (46.9%) and PDL1 (36%).(95) Only one phase II trial and only one case report on immunotherapy in uterine sarcomas have been published so far.(96, 97) In twelve uLMS patients treated with PD-1 inhibitor nivolumab 3 mg/kg every two weeks, no objective responses were found and median PFS was only 1.8 months. Due to a lack of clinical benefit the second part of the study wasn't opened. Archival samples were available for 83% of patients. PD-1 (>3% of cells), PD-L1, and PD-L2 (>5% and >10% of tumour cells, respectively) expression were observed in 20%, 20%, and 90% of samples, respectively.(97) Very recently, a phase II trial testing nivolumab in all types of uterine cancer, including uLMS, HG-ESS and HGUS, started recruitment.(NCT03241745)

Other ongoing immunotherapy studies are not specifically focused on uterine sarcomas. An active phase II study is investigating the role of the anti-PD-1 antibody, pembrolizumab, in patients with advanced soft tissue and bone sarcomas.(NCT02301039) Furthermore, a phase I-II trial combining pembrolizumab with doxorubicin in advanced or metastatic STS is open (NCT02888665), as is a phase II study of Talimogene Laherparepvec (T-VEC) combined with pembrolizumab.(NCT03069378) In the neoadjuvant setting, anti-PD-L1 (Durvalumab/MEDI4736) plus anti-CTLA-4 (Tremelimumab) and radiation is tested for high risk STS.(NCT03116529). The combination of tyrosine kinase inhibitor axitinib and pembrolizumab is currently tested in specific types of STS, including LMS after failure of anthracyclines.(NCT02636725) As a first line therapy, the combination of trabectedin, nivolumab and anti-CTLA-4 ipilimumab is under investigation in a dose finding phase I-II study for advanced STS.(NCT03138161)

3.3.2. Targeted therapy

Targeted therapy refers to systemic therapy directed to specific elements or pathways crucial for cancer cells to survive. Only results of a few trials or subgroup analyses in uterine sarcomas are available (table 3). Some categories of targeted therapy can be distinguished:

3.3.2.1. Tyrosine kinase inhibitors directed against a.o. vascular endothelial growth factor receptor (VEGFR) and platelet derived growth factor receptor (PDGFR):

A subgroup analysis on 34 patients with uterine sarcomas treated the phase II pazopanib trial or PALETTE trial showed a response rate of 11%, median PFS of 3.0 months and OS of 11.1 month, which was worse compared to the non uterine STS types (mPFS 4.5 months, mOS 17.5 months).(98) A randomized phase II study comparing pazopanib combined with gemcitabine to gemcitabine-docetaxel in STS is currently ongoing.(NCT01593748) Sunitinib 50 mg OD 4 weeks on - 2 weeks of, failed to achieve a sufficient number of objective responses (8.7%) or sustained disease stabilization (mPFS 1.5 months and 6 months PFS rate 17.4%) as second- or third-line treatment for uterine leiomyosarcoma.(99) Cabozantinib, targeting MET as well as VEGFR, is currently under investigation as maintenance therapy after chemotherapy in metastatic HGUS, adenosarcomas, and HG ESS.(NCT01979393)

3.3.2.2. VEGF trap/antibody

VEGF trap aflibercept 4 mg/kg iv every 2 weeks showed similar disappointing results in patients with uLMS or carcinosarcomas of the uterus: no objective responses were observed, median PFS was 1.8 months and the 6 months PFS was 17%.(100) The addition of VEGF antibody bevacizumab to gemcitabine-docetaxel did not improve outcome.(58)

3.3.2.3. PDGFR antibody

As described above, in a randomized phase II trial, addition of PDGFR antibody olaratumab improved OS by more than 10 months.(66) The phase III trial is ongoing.[NCT02451943] Currently, the addition of olaratumab to gemcitabine-docetaxel is investigated in a phase Ib-II trial in STS.(NCT02659020)

3.3.2.4. Other targets

Although the PI3K/mTOR pathway has been recognized as a potential target for uLMS in preclinical work, no series or (ongoing) trials have been found for US.(101) The same is the case for VIPR2, a gene affected in 96% of 84 uLMS samples which seems to act as a tumor suppressor gene.(102)

3.3.2.5. Epigenetic modulators

Histone deacetylase inhibitor panobinostat in a phase II trial for STS with 10 LMS and 3 ESS patients did not result in any objective responses but 2/10 LMS and 2/3 ESS patients had prolonged stable disease for more than six months. Pabinostat was poorly tolerated with the need of dose reduction in up to one third of the patients due to thrombocytopenia, anaemia, lymphocytopenia, fatigue and QTc prolongation.(103) Aurora A kinase inhibitor alisertib was not effective in 21 uLMS patient as no objective responses or prolonged stable disease were seen. Median PFS and OS were 1.7 and 14.5months, respectively.(104)

In conclusion, currently, with respect to targeted agents, only pazopanib has a place in the treatment of US after failure of at least anthracyclines. Based on promising phase II results and awaiting the outcome of the phase III study, in some countries olaratumab can be added to doxorubicin in first line treatment.

TABLE 3	population	n (%(u)LMS)	RR (%)	3mo PFR (%)	6mo PFR (%)	PFS (months)	OS (months)
nivolumab(97)	uLMS	12	0	-	-	1.8	-
pazopanib(98)	US	44	11	-	-	3	17.5
regorafenib vs. placebo (105)	STS, 1 cohort LMS	56 LMS of who 22 uLMS	0	57 vs. 25	21 vs. 7	3.7 vs. 1.8	21 vs. 9.1
sunitinib(99)	uLMS	23	8.7	-	17.4	1.5	15.1
thalidomide(106)	uLMS	30	0	-	-	1.9	8.3
aflibercept(100)	uLMS	41	0	-	17	1.8	18.1
alisertib(104)	uLMS	21	0		0	1.7	14.5

Table 3. Systemic non-cytotoxic treatment trials in advanced or metastatic uterine sarcomas.

M; median, mo; months, RR; response rate, PFS; progression free survival, OS; overall survival, US; uterine sarcomas, uLMS; uterine leiomyosarcoma, LMS; leiomyosarcoma, STS; soft tissue sarcoma.

4. Future directions and conclusion

Uterine sarcomas encompass a rare group of diseases with a dismal prognosis of aggressive subtypes. For the choice of systemic treatments, part of the difficulty is the recognition of the specific subtype of uterine sarcoma and an adequate pathology diagnosis, including molecular analyses. Very recently, new genetic and immunological differences between uLMS, ESS and HGUS were shown. Gene expression and immunohistochemical analyses revealed the presence of high numbers of tumor-associated macrophages (TAMs) in HGUS, which makes HGUS patients suitable candidates for therapies targeting TAMs. Furthermore, a high genomic instability of HGUS and downregulation of several TP53-mediated tumor suppressor genes, such as NDN, CDH11, and NDRG4 were proven. Moreover, it was demonstrated that HGUS carry somatic mutations in several oncogenes and tumor suppressor genes implicated in RAS/PI3K/AKT/mTOR, ERBB3, and Hedgehog signaling for which targeted therapies exist.(107)

After the primary diagnosis and treatment by gynaecologists and their multidisciplinary teams, early involvement of sarcoma specialists is necessary. Many centres are only treating a few patients per year. All together, this makes it difficult to improve the diagnostic and treatment trajectory of US patients. Centralisation of care and the timely collaboration between gynaecological oncologists and sarcoma specialists might help to deliver the best knowledge, experience and trial availability to US patients. By now, despite many attempts to improve the outcome by systemic treatments, the prognosis, both after primary diagnosis and in case of metastatic disease, remains poor. The observation of heterogeneity within uterine sarcoma subtypes warrants a personalized treatment approach. Further studies with realistic analysis of patients numbers are needed to improve patient outcome. Given the experiences so far, this is a challenge at a global level.

Conflicts of interest statement

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