Current and future options in the management and treatment of uterine sarcoma

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***Abstract*:** Uterine sarcomas are rare aggressive mesenchymal tumours with limited prognosis. They encompass various histological subtypes such leiomyosarcoma, endometrial stromal sarcoma and undifferentiated sarcomas with different surgical and medical strategies. Current evidence of surgery, adjuvant and palliative therapy is reported.

Keywords: chemotherapy, endometrial stromal sarcoma, surgery, uterine leiomyosarcoma, uterine sarcoma

Introduction

Uterine sarcomas are uncommon aggressive mesenchymal tumours, which comprise only about 3% of all uterine malignancies [D'Angelo and Prat, 2010]. The incidence of uterine sarcomas varies between 0.5 and 3.3 cases per 100,000 women per year [Harlow *et al.* 1986]. Uterine sarcomas include different histological entities. The most frequent type is leiomyosarcoma (LMS) in about 60% of cases, followed by endometrial stromal tumours (ESS), undifferentiated uterine sarcomas (UUS), and pure heterologous sarcomas. Mixed epithelial and mesenchymal tumours are adenosarcoma (with and without sarcomatous component) and carcinosarcoma (mixed mullerian tumours). Carcinosarcoma are of epithelial origin, as shown by *in vitro* data, immunohistochemical and molecular studies [Amant *et al.* 2005]. Therefore, uterine carcinosarcoma are counted as undifferentiated epithelial uterine carcinoma and should not be classified into the sarcoma group.

In this paper we therefore focus on mesenchymal uterine tumours like LMS, endometrial stromal sarcoma and undifferentiated stromal sarcoma.

Uterine LMS

LMS represents the most common uterine sarcoma. It accounts for about 1% of all uterine malignancies [Amant *et al.* 2005]. The incidence of LMS in series of hysterectomies performed for presumed uterine leiomyomas is approximately 0.1–0.3% [Leibsohn *et al.* 1990]. In most cases firm diagnosis cannot be made preoperatively. Most women with LMS lack symptoms or present with a rapidly enlarging pelvic mass [Ramondetta, 2006; Zivanovic *et al.* 2009; Vrzic-Petronijevic *et al.* 2006].

Some 60% of women with LMS present with a disease limited to the uterus at first diagnosis [Major *et al.* 1993]. Cure rates of these patients range from 20 to 60% depending on the success of the primary resection [Ramondetta, 2006; Gadducci A *et al.* 2008]. Relapse rate is approximately 70% for stage I and II. The site of metastasis or recurrence is often distant due to haematogenous spread into the lungs or liver [Ramondetta, 2006; Major *et al.* 1993]. Therefore, complete radiologic staging at first diagnosis and at relapse including computerized tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen and pelvis is mandatory. Although several prognostic factors in addition to tumour stage have been examined, results are inconclusive and play only a limited role for treatment decision [Ramondetta, 2006; Major *et al.* 1993; Akhan *et al.* 2005; Gadducci *et al.* 2008].

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Surgical treatment

The cornerstone of the treatment in LMS is surgery. The resection of the localized disease by hysterectomy is regarded as gold standard. Total abdominal hysterectomy and bilateral salpingo-oophorectomy is considered to be the standard surgical treatment [Vrzic-Petronijevic *et al.* 2006; Ramondetta L *et al.* 2006; Gadducci A *et al.* 2008, Zivanovic *et al.* 2009]. Pelvic and para-aortic lymphadenectomy is not routinely indicated. The incidence of lymphatic spread is only about 3% in early stage uterine LMS [Gadducci *et al.* 2008; Vrzic-Petronijevic *et al.* 2006; Giuntoli *et al.* 2003; Leitao *et al.* 2003]. However, lymph-node involvement is often present in advanced disease. Ovarian preservation can be considered in premenopausal patients with early stage LMS of the uterus [Gadducci A *et al.* 1996a]. Many LMS are diagnosed after surgical intervention of presumed leiomyoma or hysterectomy. Morcellation of the tumour or uterus in total, for example, during laparoscopic assisted supracervical hysterectomy increases the rate of the abdominopelvic dissemination causing an iatrogenic advanced stage disease. This translates to a worse progression-free survival (PFS) and overall survival (OS). Thus, before performing surgery with morcellation, women have to be informed in detail about the possibility of tumour dissemination and prognosis deterioration *via* iatrogenic advanced stage disease [Park *et al.* 2011].

Medical therapy

Uterine LMS is an aggressive malignancy with a high risk of local and distant relapse even in completely resected tumours. Postoperative pelvic radiation therapy has been compared with observation for localized disease of uterine sarcoma including LMS stage I or II [Reed *et al.* 2008]. Neither PFS, nor OS nor pelvic control was improved by radiotherapy. Therefore, radiation therapy is not indicated in patients with stage I or II LMS after complete resection.

So far, only one randomized trial for localized LMS has been performed comparing doxorubicin (60 mg/m², every 3 weeks for 8 courses) with observation [Omura *et al.* 1985]. Differences in PFS and OS were not significant, but there was a trend favouring chemotherapy (relapse rate 44% *versus* 61%). A recently updated meta-analysis showed an improvement of prognosis by chemotherapy; mainly combination chemotherapies including doxorubicin and ifosfamid regimen in patients with complete resection of soft tissue sarcoma were reported [Pervaiz *et al.* 2008]. But because this meta-analysis included several non-LMS trials it is difficult to draw any definitive conclusion for this entity.

A prospective phase II trial testing the combination chemotherapy of gemcitabine and docetaxel followed by doxorubicin in stage I/II disease reported promising results regarding activity (2 year PFS: 78%) [Hensley *et al.* 2013]. The combination of carboplatin and pegylated liposomal doxorubicin also demonstrated activity in another phase II trial [Harter *et al.* 2011].

Adjuvant chemotherapy with doxorubicin, ifosfamide and cisplatin followed by radiotherapy *versus* radiotherapy alone in patients with localized uterine sarcomas was evaluated in another randomized clinical phase III trial. A significant improvement of the 3-year PFS was detected in the cohort treated with combined modalities: 51% [95% confidence interval (CI): 34–69%) *versus* 40% (95%CI: 25–58%) in the radiotherapy group ($p = 0.048$). OS differences were not significant. However, this regimen showed remarkable toxicity including two therapy related fatal events in the combined modality arm [Pautier *et al.* 2012].

Treatment of recurrent LMS

If surgery remains a treatment option at advanced stage or at relapse has to be discussed on an individual basis [Leitao *et al.* 2003, 2012; Zivanovic *et al.* 2009].

There is a lack of clinical trials that have dealt only with pure recurrent LMS sarcoma. Most available data are from studies with metastatic uterine sarcoma and recurrence. This is probably explained by the rarity of the disease.

A randomized phase II clinical trial compared gemcitabine *versus* gemcitabine and docetaxel in the metastatic situation of soft tissue sarcomas. The trial's conclusion was that the combination therapy was superior to monochemotherapy with gemcitabine. The median PFS was 6.2 months for gemcitabine–docetaxel *versus* 3.0 months for gemcitabine ($p = 0.02$). The median OS was 17.9 months for combination therapy *versus* 11.5 months for monochemotherapy ($p = 0.03$). However, more than 40% of the patients had to stop therapy as result of toxicity [Maki *et al.* 2007].

A randomized phase II trial included patients with advanced or recurrent liposarcoma or LMS after failure of prior antracycline and ifosfamide therapy. Compared were two schedules with trabectidin monotherapy: 24-hour intravenous of 1.5 mg/m² infusion once every 3 weeks *versus* 3-hour infusion of 0.58 mg/m² weekly. This clinical trial showed a clinical benefit for trabectidin given to patients in the 24 hours regimen. Median PFS was 3.3 months *versus* 2.3 months [hazard ratio (HR): 0.755; 95%CI: 0.574–0.992; p = 0.0418]. Median OS was 13.9 months *versus* 11.8 months (HR: 0.843; 95%CI: 0.653–1.090; p = 0.1920) [Demetri *et al.* 2009].

The only randomized double blind, placebo-controlled phase III trial in patients with metastatic and recurrent nongastrointestinal stromal tumour soft tissue sarcoma was a trial with pazopanib. It showed a significant increase in PFS by a median of 3 months compared with placebo (4.6 months *versus* 1.6 months; HR: 0.31, 95%CI: 0.24–0.40; $p < 0.0001$). OS was 12.5 months for pazopanib *versus* 10.7 months with placebo (HR: 0.86, 95%CI: 0.67–1.1; $p = 0.25$). Pazopanib is a new oral treatment option, after previous chemotherapy for metastatic nongastrointestinal stromal tumour, nonadipocytic soft tissue sarcoma [Van der Graaf *et al.* 2012].

Ridaforolimus is a mammalian target of rapamycin (mTOR) inhibitor, which was investigated in a clinical phase II trial including patients with advanced bone and soft tissue sarcomas. It showed a good clinical benefit rate (CBR) defined as complete response (CR), partial response (PR) or stable disease (SD) of ≥16 weeks. In the subgroup of LMS was the highest CBR reported with about 33.3% [Chawla *et al.* 2012]. A subsequent phase III trial investigated the efficacy of ridaforolimus as maintenance therapy after chemotherapy. The study met its primary endpoint of independent radiologic assessed PFS (14.6 *versus* 17.7 weeks; HR: 0.72, p = 0.0001). However 52% experienced stomatitis as side effect of ridaforolimus [Chawla *et al.* 2011]. The final publication including mature data for OS is awaited to discuss the role of ridaforolimus in the treatment of sarcoma.

A nonrandomized multicentre phase II clinical trial with eribulin in patients with advanced or metastatic of high and intermediate grade soft tissue sarcoma has achieved the endpoint of the trial (12 weeks PFS). Patients with adipocytic sarcoma and LMS had the best responses [Schöffski *et al.* 2011].

The combination of carbopatin and pegylated liposomal doxorubicin seems to be favourable in terms of toxicity and safety with a good efficacy even in advanced and recurrent situations. The median PFS was 8.6 months (95% CI: 6.4–10.4). The median OS was 29.5 months and 77% of the patients had reached 12 months OS [Harter *et al.* 2011].

Another phase II trial (total 113 patients including 32 LMS) demonstrated the superiority of the combination therapy with dacarbacine and gemcitabine compared with gemcitabine alone in patients with previously treated soft tissue sarcoma. The median PFS was 4.2 months *versus* 2 months (HR: 0.58; 95%CI: 0.39–0.86; p = 0.005). The median OS was 16.8 months *versus* 8.2 months (HR: 0.56; 95%CI: 0.36–0.90; p = 0.014) [Garcia del Muro *et al.* 2011]. Table 1 summarizes the most clinical trial to this topic.

ESS

This form of uterine sarcoma is a rare uterine tumour accounting for 0.2–1% of all uterine malignancies and 6–20% of all uterine sarcomas [Koss *et al.* 1965; Harlow *et al.* 1986]. Due to the rarity of this type of sarcoma, there are limited data regarding this tumour entity. Most of available data are retrospective analysis based on small number of patients. ESS affects younger women with a mean age of between 42 and 58 years [Tavassoli and Deville, 2003]. ESS is an indolent tumour with local recurrences and distant metastasis can occur even 20 years after first diagnosis [Gadducci *et al.* 2008].

The traditional classification of ESS into low-grade and high-grade categories is obsolete. It is necessary to distinguish between endometrial stromal sarcoma and undifferentiated uterine sarcoma. The usual clinical presentation of ESS is abnormal uterine bleeding that occurs in about 90% of women and 70% of cases show uterine enlargement. They can present with pelvic pain and dysmenorrhea, and about 30–50% of the ESS have extra uterine spread at the time of the diagnosis [Tavassoli and Deville, 2003]. Although the main tumour mass is almost intramyometrial, most ESS involve the endometrium and uterine curettage may be helpful in preoperative diagnosis [Ganjoei *et al.* 2006; Jin *et al.* 2010]. Due to the great similarity of ESS with normal endometrium,

Table 1. Overview of clinical trials with sarcoma.

Reference	Entities	Stage	Trial-phase	Design	Progression-free survival	Overall survival
Omura *et al.* [1985]	Uterine sarcoma	I, II	II *n* = 156	adriamycin 60 mg/m² q 21 *versus* observation	no significant difference	73 months *versus* 55 months; *p* = ns
Pautier *et al.* [2012]	Uterine leiomyosarcoma	I, II	II *n* = 81	doxorubicin 50 mg/m² d1, ifosfamide 3 g/m²/day d1–2 and cisplatin 75 mg/m² d3,q 21 -> RT *versus* RT	3 year PFS: 51% *versus* 40%; *p* = 0.0048	3-year OS: 81% *versus* 69%; *p* = 0.41
Hensley *et al.* [2013]	Uterine leiomyosarcoma	I, II	II *n* = 47	gemcitabine 900 mg/m² days 1 and 8 plus docetaxel 75 mg/m² d8 -> doxorubicin 60 mg/m² q21	2-year PFS: 78%	
Harter *et al.* [2011]	Uterine/ ovarian sarcoma	I–IV and relapse	II *n* = 40	Pegylated liposomal doxorubicin 40 mg/m² plus carboplatin AUC 6 q28	8.6 months	29.5 months
Demetri *et al.* [2009]	Lipo-/leiomyo-sarcoma	relapsed	II *n* = 270	trabectidin 1,5 mg/m²(q21, 24 h) *versus* trabectidin 0.58 mg/m² (q1W, 3 h)	3.3 months *versus* 2.3 months; *p* = 0.0418	13.9 months *versus* 11.8 months, *p* = 0.1920
Maki *et al.* [2007]	Soft tissue sarcoma	metastatic	II *n* = 122	gemcitabine 900 mg/m² days 1, 8 plus docetaxel 75 mg/m² d8, q21 *versus* gemcitabine 1,200 mg/m² (1+8,q3w)	6.2 months *versus* 3.0 months; *p* = 0.02	17.9 months *versus* 11.5 months; *p* = 0.03
Garcia del Muro *et al.* [2010]	Soft tissue sarcoma	advanced	II *n* = 113	dacarbacine 500 mg/m², gemcitabine 1,800 mg/m²(q2w) *versus* dacarbacine 1,200 mg/m² (q21	16.8 months *versus* 8.2 months; *p* = 0.014.	4.2 months *versus* 2 months; *p* = 0.005
Van der Graaf *et al.* [2012]	Soft tissue sarcoma	metastatic	III *n* = 362	pazopanib 800 mg once daily *versus* placebo	4.6 months *versus* 1.6 months; *p* < 0.0001	12.5 months *versus* 10.7 months; *p* = 0.25
Chawla *et al.* [2011]	Soft tissue + bone sarcoma	relapsed, maintenance	III *n* = 711	ridaforolimus 12.5 mg (d1-d5,q2w) *versus* placebo	14.6 *versus* 17.7 weeks; *p* = 0.0001	21.4 months *versus* 19.2 months; *p* = ns
Schöffski *et al.* [2011]	Soft tissue sarcoma	metastatic	II *n* = 128	eribulin 1.4 mg/m² (d1-d8,q21)	2.1–2.6 months (depending on histologic subtype)	6 months OS: 52.9–86.8% months (see above)

ns, not significant; OS, overall survival; PFS, progression-free survival.

it can be difficult to diagnose ESS on curettage fragments and the definitive diagnosis can be made only on a hysterectomy specimen.

Surgical treatment

Surgical treatment of ESS includes an exploratory laparotomy, total abdominal hysterectomy and bilatreal salpingo-oophorectomy, omental biopsy and aspiration of abdominal fluid for cytologic evaluation [Berchuck *et al.* 1990; Ramondetta, 2006; Gadducci *et al.* 2008; Li *et al.* 2008; Weitmann *et al.* 2001, 2002]. Immunohistochemical studies showed a rich expression of oestrogen and progesterone receptors (ER and PgR), as they are also hormonally responsive. Therefore a hormone substitution after surgery might be contraindicated [Leath *et al.* 2007; Grimer R *et al.* 2010].

However, several studies failed to show that bilateral salpingo-oophorectomy affects time for recurrence or OS in stage I disease [Li *et al.* 2005; Amant *et al.* 2007; Gadducci *et al.* 1996b; Chu *et al.* 2003; Chan *et al.* 2008]. Regarding the adverse effects of early surgical menopause, preservation of the ovarian function may be an option for premenopausal women with stage I disease [Li *et al.* 2005].

There are various rates of lymph node involvement reported in ESS showing up to 10% nodal metastases. Whilst removal of obviously affected or enlarged lymph nodes is a widely accepted procedure, systematic pelvic and para-aortic lymphadenectomy in clinically negative nodes as routine staging procedure in a disease with mainly hematologic metastases is still under discussion and not recommended by many authors [Chan *et al.* 2008; Reich *et al.* 2005; Riopel 2005]

Adjuvant therapy

So far, adjuvant radiotherapy is ineffective in endometrial stromal sarcoma stage I/II [Reed, 2008]. Standard of care in patients with stage I or II is careful follow up. In advanced stages, endocrine treatment might be an option in patients with steroid-positive tumours [Amant *et al.* 2005]. Until today, the role of adjuvant chemotherapy is undefined. Pure ESS studies are lacking and ESS are mostly included in other series as a subentity. Most results from those trials, as explained above in the LMS section. might be an option for such tumours. However, if there is an indication for systemic treatment, first choice is always endocrine therapy. Medroxyprogesterone (MPA) and aromatase (AI) inhibitors showed good efficacy and led to sustained disease control in some advanced and metastatic cases [Pink *et al.* 2006; Lehrner *et al.* 1979].

Treatment of recurrent ESS

ESS recurs most commonly in the abdomen/pelvis (40–50%) followed by lung (in approximately 25% of cases) [Cheng *et al.* 2011; Beck *et al.* 2012]. Late recurrences are common even with early stage disease. Treatment for recurrent ESS depends on prior endocrine therapy. In recurrent patients without any prior endocrine therapy, endocrine agents such as MPA and AI are the primary treatment.

In patients who recur after or during endocrine therapy, cytotoxic chemotherapy is the first choice. Patients who progress following prior treatment (including endocrine therapy in the adjuvant or first-line metastatic setting) are candidates for cytotoxic chemotherapy. The approach to these patients is similar to those patients with metastatic or recurrent LMS; available treatment combinations include gemcitabine plus docetaxel and doxorubicin-based regimens

UUS

This entity of uterine sarcoma is high grade epithelioid or spindle cell sarcoma. It represents an independent uterine tumour entity. It accounts less than 5% of all uterine sarcomas [Ramondetta, 2006; Abeler *et al.* 2009; Nordal *et al.* 1997]. This type of tumour grows quickly and has high malignancy characteristics which result in a poor prognosis. The 5-year OS rate has reached 25–55% [Gadducci *et al.* 1996b, 2008; Berchuck *et al.* 1990; Koivisto-Korander *et al.* 2008].

Surgical treatment

Despite limited evidence, recommended surgical treatment for UUS is total abdominal hysterectomy and bilateral salpingo-oophorectomy [Ramondetta, 2006; Gadducci *et al.* 2008; Vrzic-Petronijevic *et al.* 2006; Kanjeekal *et al.* 2005; Kokawa *et al.* 2006]. The value of lymphadenectomy remains controversial, similar to the surgical treatment of ESS [Gadducci *et al.* 1996b; Ramondetta, 2006; Goff *et al.* 1993; Shah *et al.* 2008]

Adjuvant therapy

So far, conclusive data are missing. The main risk is haematogenous spread and chemotherapy

might be an option. Doxorubicin and/or Ifosfamid are under discussion, analogous to other sarcomas [Tierney JF *et al.* 1995; Hyman *et al.* 1985]. USS might be treated with the same drugs as soft tissue sarcoma at other sites

Treatment of recurrent UUS

No randomized trials have dealt only with this type of uterus sarcomas. The therapy of recurrence is similar to soft tissue sarcomas.

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