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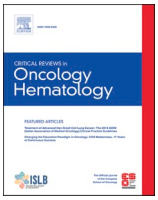

The biology and treatment of leiomyosarcomas

William G.J. Kerrison [a], Khin Thway [a,b], Robin L. Jones [b,c], Paul H. Huang [a,*]

[a] Division of Molecular Pathology, The Institute of Cancer Research, London, United Kingdom
[b] The Royal Marsden NHS Foundation Trust, London, United Kingdom
[c] Division of Clinical Studies, The Institute of Cancer Research, London, United Kingdom

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ABSTRACT

Leiomyosarcoma (LMS) is a soft tissue sarcoma of smooth muscle origin that can arise in multiple anatomical sites and is broadly classified as extra-uterine LMS or uterine LMS. There is substantial interpatient heterogeneity within this histological subtype, and despite multi-modal therapy, clinical management remains challenging with poor patient prognosis and few new therapies available. Here we discuss the current treatment landscape of LMS in both the localised and advanced disease setting. We further describe the latest advances in our evolving understanding of the genetics and biology of this group of heterogeneous diseases and summarise the key studies delineating the mechanisms of acquired and intrinsic chemotherapy resistance in this histological subtype. We conclude by providing a perspective on how novel targeted agents such as PARP inhibitors may usher in a new paradigm of biomarker-driven therapies that will ultimately impact the outcomes of patients with LMS.

1. Introduction

Leiomyosarcoma (LMS) is one of the most common soft tissue sarcoma (STS) subtypes, occurring more frequently in middle-aged or older adults, and with a slight female predominance (Kasper et al., 2021). It is thought to form from smooth muscle or its precursor cells and can therefore arise almost anywhere in the body, but most frequently in the retroperitoneum, extremities or uterus. The disease is often divided into extra-uterine LMS (arising in the retroperitoneum, walls of blood vessels, gastrointestinal tract, extremities or subcutaneously) or uterine LMS as the two groups have distinct clinicopathological characteristics (Kasper et al., 2021; Bathan et al., 2013; Smrke et al., 2021).

LMS is a particularly aggressive malignancy with distant metastases occurring in approximately half of all patients despite initial local control with resection (Penel et al., 2009). Prognosis is based on both tumour staging and anatomical location, with ten year metastatic rate ranging from 31% in extremities, 58% in abdomen and 53–71% in the uterus (Gladdy et al., 2013; Mbatani et al., 2018). As with other STS subtypes, the major clinicopathological factors which predict LMS patient outcomes are histological grade, tumour size and depth (Serrano and George, 2013). LMS are graded according to the three-tiered Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading system which considers tumour differentiation, extent of necrosis and mitotic count (Guillou et al., 1997). Uterine LMS tumours are not graded due to the limited evidence that tumour grade correlates with patient outcome and therefore, the International Federation of Gynaecology and Obstetrics (FIGO) staging system used for uterine LMS diagnosis does not account for tumour grade (Roberts et al., 2018). It is well recognised that there is substantial histological, clinical and molecular heterogeneity within LMS which is reflected in the wide ranging clinical responses and survival outcomes observed in patients (Lee et al., 2019a; Merry et al., 2021; Thway, 2009; Anderson et al., 2021).

2. Histological classification of LMS

Several histological variants exist for LMS which can be classified into spindle, myxoid and epithelioid variants, although occasionally a mix of these histotypes can be observed in the same tumour (Thway, 2009; Oliva, 2015). Well-differentiated LMS tumours commonly show spindle type histological characteristics analogous to smooth muscle, and are composed of elongated spindle cells arranged in intersecting fascicular bundles with eosinophilic cytoplasm and variable numbers of pleomorphic cells (Demicco et al., 2015). Myxoid LMS tumours contain scant cytoplasm and nuclei of oval, spindle or stellate morphology and are often hypocellular, while epithelioid LMS tumours are often hypercellular, arranged in nests or sheets with eosinophilic cytoplasm and prominent cytologic atypia (Oliva, 2015). Biomarkers of smooth muscle differentiation are used to aid in the diagnosis of LMS as most tumours

* Correspondence to: Institute of Cancer Research, 15 Cotswold Road, Sutton SM2 5NG, United Kingdom.
E-mail address: paul.huang@icr.ac.uk (P.H. Huang).

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show expression of α-smooth muscle actin (α-SMA), desmin and h-caldesmon, of which α-SMA is most commonly observed from immunohistochemical (IHC) staining across LMS tumours (Demicco et al., 2015). In a cohort of 202 non-uterine and 181 uterine LMS samples, 91%, 74% and 78% of tissues displayed α-SMA, desmin and h-caldesmon expression respectively (Demicco et al., 2015). However, there are no biomarkers exclusive to smooth muscle, and expression of these markers can be observed in other tissues and neoplasms, meaning that IHC staining for smooth muscle markers should be interpreted with caution (Serrano and George, 2013).

In addition to well-differentiated tumours, LMS can also present as moderately or poorly differentiated, and display decreasing levels of smooth muscle characteristics (Oliva, 2015). Some extremely poorly differentiated tumours are occasionally misdiagnosed as undifferentiated pleomorphic sarcomas (UPS), having lost common smooth muscle markers such as α-SMA, desmin and h-caldesmon (Oliva, 2015; Demicco et al., 2015). Additionally, a significantly higher proportion of recurrent or metastatic LMS tumours are moderately or poorly differentiated compared to primary LMS tumours which show higher proportions of well-differentiated tumour (Demicco et al., 2015).

Based on histology, uterine LMS can often be difficult to distinguish from benign myometrial leiomyomas, and the criteria for differential diagnoses are controversial, such as number of acceptable mitoses before a tumour is considered malignant and degree of cellular atypia (Zhang et al., 2021; Sanada et al., 2022; Zheng et al., 2020). Due to the difficulty in distinguishing malignancy, non-uterine smooth muscle tumours are generally considered to be malignant with any amount of mitotic activity, as benign leiomyomas very rarely occur in extra-uterine sites (Kostov et al., 2021; D'Angelo and Prat, 2010). Some reports outline mitotic activity criteria for malignancy which is different depending on histological variants, set as at least ten, four or two mitoses per ten high-power fields for spindle, epithelioid and myxoid variants respectively (Oliva, 2015; D'Angelo and Prat, 2010).

3. Genetics of LMS

Karyotyping of uterine LMS samples have shown no recurrent aberrations at the chromosomal level, while DNA copy number alteration (CNA) analysis demonstrates a complex genetic landscape with the extent of cytogenetic changes and copy number gains showing an association with tumour evolution and worse survival (Cuppens et al., 2018; Raish et al., 2012). Further genomic studies of LMS have shown that genetic losses are often detected in certain chromosomal regions such as 10q11–21.2 encoding *PTEN*, 13q14.3-q21.1 encoding *RB1* and 17p13 which encodes *TP53* (Cuppens et al., 2018; Chudasama et al., 2018; Nacev et al., 2022). Taken together, inactivating genetic aberrations including mutations and gene deletions in *TP53* and *RB1* are almost universally seen in LMS (92% and 94% respectively) while 57% of LMS display inactivating aberrations in *PTEN* (Chudasama et al., 2018). Other studies have showed that aberrations in the RB1-cyclin D1 pathway including *RB1*, *CCND1*, *CCND3* and *CDKN2A* are seen in approximately 90% of LMS tumours and is associated with a worse prognosis (Anderson et al., 2021; Dei Tos et al., 1996; Yang et al., 2009). The Cancer Genome Atlas (TCGA) study found *PTEN* gene mutations in 5% of LMS samples, deep PTEN gene deletions in 13% of LMS samples and a further 68% of LMS samples showed shallow *PTEN* gene deletions (Abeshouse et al., 2017). Additionally, in a small cohort of 17 LMS tumours, *PTEN* loss was associated with a poorer prognosis for LMS patients (Hu et al., 2005). While far less common than *PTEN* alterations, gain of function aberrations in *PIK3CA* can also be observed in a small subset of LMS (Nacev et al., 2022).

Deregulation in DNA damage repair pathways (DDR), especially homologous recombination (HR) repair, and DNA damage tolerance pathways leads to increased genomic instability and thus promotes cancer progression (Bouwman and Jonkers, 2012). Germline heterozygous mutations in BRCA1/2 genes, for example, confer a significantly increased risk of developing breast, ovarian, prostate and other cancers by pre-disposing the individual to bi-allelic loss of BRCA1/2 function via loss of heterozygosity (Rebbeck et al., 2018). Analysis of a pan-cancer cohort showed that uterine LMS harboured HR deficiency including alterations in BRCA1/2, the majority of which was due to somatic homozygous deletion (Jonsson et al., 2019). In a cohort of 80 uterine LMS patients, 5% displayed a homozygous deletion of BRCA2 while another LMS cohort of 49 uterine or non-uterine tumours identified gene deletions in multiple components of the HR pathway, including *PTEN, BRCA2, ATM, CHEK1, XRCC3, CHEK2, BRCA1* and *RAD51* with a prevalence of 57%, 53%, 22%, 22%, 18%, 12%, 10% and 10% respectively (Chudasama et al., 2018; Hensley et al., 2020). BRCA1/2 deletions were identified in 50% of the uterine cohort, 10% and 40% being homozygous or hemizygous BRCA1/2 deletions respectively (Chudasama et al., 2018).

Genomic scarring, a particular pattern of mutations occurring when double strand breaks (DSB) cannot be repaired via HR, was detected in most LMS, suggesting impaired HR activity (Chudasama et al., 2018; Vyse et al., 2021). Furthermore in an analysis where 214 STS patient specimens from the Cancer Genome Atlas (including LMS) were assigned a HR deficiency score, taking into account loss of heterozygosity, telomeric allelic imbalance and large-scale state transitions, the authors showed that patients with a low HR deficiency score had a significantly better prognosis compared to patients with a high HR deficiency score (Li et al., 2020). HR deficiency, as defined by the HR deficiency score was also detected in a panel of STS cell lines, including the uterine LMS model SK-LMS-1 (Li et al., 2020). In a larger study including 121 uterine LMS patients, 30 (25%) patients displayed DDR alterations which is higher than the 14% observed in a non-uterine LMS cohort of 90 patients which suggests that uterine LMS tumour might be particularly susceptible to therapeutic targeting of the DDR pathway (Rosenbaum et al., 2019). Meanwhile Nacev et al. showed that 24% of 165 uterine LMS tumour samples and 10% of 125 non-uterine LMS tumours display DDR gene alterations (Nacev et al., 2022). LMS patients with alterations in DDR associated genes were found to have a worse prognosis compared to LMS patients without these DDR gene alterations, and non-BRCA gene alterations in particular showed a significant negative correlation with overall survival (OS) (Rosenbaum et al., 2020).

Genomics can also be used to distinguish between benign and malignant smooth muscle tumours. For example, genomic hybridisation array analysis can be used to distinguish between leiomyomas and LMS by assigning a genomic rearrangement score where smooth muscle tumours of unknown malignant potential (STUMP) with high rearrangement scores have clinical characteristics of malignant LMS, while STUMPs with low scores had favourable outcomes consistent with benign leiomyomas (Croce et al., 2015; Przybyl et al., 2018).

4. Molecular classification of LMS

Utilising gene expression microarrays, three distinct transcriptomic subgroups were identified from a cohort of 51 LMS tumours (Beck et al., 2009). The first subgroup, termed 'muscle-enriched LMS' was shown to have elevated expression of genes involved in muscle differentiation and function such as *CALD1* and *ACTG2*. The majority of tumours in this group showed a loss of 16q24, containing the *FANCA* gene, which is involved in DNA repair, and loss of 1p36, containing *PRDM16*, the loss of which causes muscle differentiation (Benitez et al., 2018; Seale et al., 2008). The second group presented by Beck et al. had elevated or differential expression of genes relating to protein metabolism and regulation of cell proliferation, while the third group was enriched for the elevated or differential expression of genes associated with extracellular proteins, wound response components, and protein synthesis (Beck et al., 2009). No significant difference in tumour grade was found between each subgroup. Subgroup 1 and 2 were found to have a higher percentage of non-uterine cases, making up 91% and 75% of each subgroup respectively while Subgroup 3 showed an even distribution of

both uterine and non-uterine cases.

In a separate transcriptomic study of 37 LMS patient tumours, three subgroups were again identified (Chudasama et al., 2018). Gene ontology analysis revealed subgroup 1 to be enriched in biological functions such as platelet degranulation, complement activation and metabolism. Subgroup 2 was characterised by an enrichment in muscle function and development processes, while subgroup 3 showed a low expression of genes which separated subgroups 1 and 2 but with slightly higher expression of genes associated with myofibril assembly, muscle filament action and cell-cell signalling. Subgroup 3 comprised of 70% of the cohort while groups 1 and 2 made up 14% and 16% of the cohort respectively. Uterine LMS tumours were not enriched or absent in any particular subgroup. The authors noted that subgroups 2 and 3 corresponded to the previously reported subgroups II and I from Beck and co-workers respectively.

In a third study performed by Hemming and co-workers, three distinct LMS transcriptomics subgroups were also identified. These subgroups were termed as conventional LMS (cLMS) which was enriched in muscle associated processes, inflammatory LMS (iLMS) which was enriched in immune markers, and uterogenic LMS (uLMS) which was enriched in a uterine-like gene expression program (Hemming et al., 2020). Finally in a fourth study, an analysis of 130 transcriptomes also revealed three distinct subgroups. Further genomic analysis showed these subgroups represent early evolutionary branches of LMS which arise from distinct lineages of smooth muscle such as vascular, digestive and gynaecological smooth muscle. The authors classed these subgroups as subtype 1 (dedifferentiated), 2a (abdominal), 2b (abdominal or extremity) which together comprised the majority of samples in the cohort, and 3 (gynaecological) (Anderson et al., 2021).

Despite the recurrent identification of three transcriptomic subgroups, the prognostic association of subgroups is not consistent between studies and after adjusting for clinicopathological variables, subgroups were not independent prognosticators of outcome. Therefore, the clinical value of transcriptomic classification remains to be determined (Merry et al., 2021; Burns et al., 2022).

5. Treatment in localised disease

The gold standard for treatment of localised disease is surgical resection with or without neo-adjuvant or adjuvant radiotherapy and/or chemotherapy (Linch et al., 2014; Casali et al., 2018). Neoadjuvant radiotherapy is widely considered standard of care for localised extremity LMS (Gennaro et al., 2021; Gingrich et al., 2017). For example, Gingrich et al. showed that 90% of patients who had received neoadjuvant radiotherapy were able to achieve resection margins without residual disease (R0) while this was reduced to 75% and 80% in the adjuvant radiotherapy and no radiotherapy treatment arms, giving an odds ratio of 1.8 for R0 margins following neoadjuvant radiotherapy (Gingrich et al., 2017).

There are, however, multiple conflicting results from clinical trials assessing the benefit of adjuvant chemotherapy (with or without radiotherapy) following surgical excision to prevent recurrence. A meta-analysis of 18 trials of 1953 STS patients (including LMS) with localised resectable tumours showed that adjuvant chemotherapy led to a small but statistically significant decrease in both local and distant recurrence with an odds ratio of 0.73 and 0.69 respectively (Pervaiz et al., 2008). Doxorubicin-based adjuvant chemotherapy reduced overall recurrence with an odds ratio of 0.69 while combination doxorubicin and ifosfamide reduced overall recurrence with an odds ratio of 0.61. For OS, doxorubicin-based adjuvant chemotherapy resulted in a non-significant decrease in mortality, although doxorubicin and ifosfamide combination showed a decrease in mortality that was significant. This benefit was not observed, however, in a pooled analysis of two trials from the European Organisation for Research and Treatment of Cancer (EORTC). From a total of 819 STS patients (including LMS) randomised to adjuvant or non-adjuvant therapeutic arms, adjuvant chemotherapy was not associated with improved outcomes in any STS subtype (Le Cesne et al., 2014). A later EORTC trial randomised 351 intermediate to high grade STS patients (including LMS) without metastasis to receive adjuvant chemotherapy following excision but no benefit in OS or relapse-free survival (RFS) was observed compared to the control cohort (Woll et al., 2012). Due to these conflicting reports, adjuvant chemotherapy is not routinely recommended. All of these trials are limited by the inclusion of heterogeneous patient populations, including tumour subtype, size, grade and anatomical location as well as small patient numbers and sub-optimal chemotherapy schedules.

The potential benefit of neoadjuvant chemotherapy is still under evaluation although current studies are similarly conflicting (Gronchi et al., 2021; Pasquali et al., 2022). Results from a randomised phase 3 trial showed that neoadjuvant chemotherapy did not lead to any complete responses and only improved OS or disease free survival (DFS) in patients treated with standard chemotherapy such as anthracyclines and ifosfamide, and not histology-driven chemotherapy with a DFS odds ratio of 0.47 (Gronchi et al., 2020). This trial had strict inclusion criteria: tumours greater than 5 cm, high grade and deep seated location.

6. First-line treatment in advanced disease

For LMS patients with advanced disease, first-line chemotherapy is used primarily for disease control and palliation but rarely with curative intent. Patients with higher grade tumours are more likely to respond to chemotherapy, with a 65% relative improvement in response for each increase in tumour grade (Sleijfer et al., 2010; Savina et al., 2017). The anthracycline doxorubicin is the most commonly used first-line therapy for advanced LMS and is one of the first agents seen to produce meaningful responses in patients with advanced disease. Response rates of 12–30% are observed in metastatic LMS patients receiving doxorubicin-based regimens (Judson et al., 2014; Tap et al., 2020; D'Ambrosio et al., 2020). Given that anthracycline-based chemotherapy is cemented as the backbone of advanced LMS management, many trials have sought to improve first-line response rates or progression free survival (PFS) by combining doxorubicin with other chemotherapeutic agents which have shown some degree of activity as monotherapies (summarised in Table 1) (Gronchi et al., 2021).

The DNA alkylating agent, ifosfamide is another standard chemotherapy for STS, showing single agent, dose dependent, response rates of 5–25% (Tascilar et al., 2007; Lorigan et al., 2007). In a retrospective analysis, it was shown that ifosfamide had limited activity in LMS and also when combined with doxorubicin showed no significant difference in OS compared to doxorubicin first-line treatment alone (Sleijfer et al., 2010). A phase 3 trial conducted by EORTC comparing doxorubicin alone versus intensified doxorubicin and ifosfamide in the first-line setting across multiple STS subtypes showed no significant difference in OS between the two arms while median PFS was higher in the combination arm versus doxorubicin alone (Judson et al., 2014). Further data from a meta-analysis of STS patients from the EORTC showed that LMS patients are less responsive to first-line treatment regimens containing ifosfamide, with response rates of 19.5% and 25.6% for doxorubicin with ifosfamide or doxorubicin alone respectively. Additionally, the study showed that LMS patients receiving doxorubicin with ifosfamide had shorter OS compared to doxorubicin monotherapy (D'Ambrosio et al., 2020).

While another alkylating agent, dacarbazine, has not been assessed as a first-line monotherapy agent in LMS, the agent has shown some activity as a first-line treatment when combined with doxorubicin in advanced LMS patients, showing an improved response rate of 30.9% compared to doxorubicin and ifosfamide (19.5%) and doxorubicin monotherapy (25.6%) (D'Ambrosio et al., 2020). It should be noted that most of the evidence for the use of dacarbazine in LMS has been retrospective in nature. Gemcitabine is another chemotherapy which has been assessed as a first-line treatment for advanced LMS and other STS subtypes, although initial results from a phase 2 trial showed minimal

Table 1
A selection of clinical trials and retrospective studies assessing systemic chemotherapies as a first line treatment for advanced LMS. LMS; leiomyosarcoma, uLMS; uterine leiomyosarcoma, mPFS; median progression-free survival, mOS; median overall survival.

Reference	Type of study	N	Subtypes	Treatment	Response rate	mPFS (months)	mOS (months)
(Pautier et al., 2022)	Randomised phase 3	150	LMS	Doxorubicin & trabectedin vs doxorubicin	Uterine 36% vs 15%; non-uterine 37% vs 12%	6.2 vs 12.2	Not available
(Pautier et al., 2021)	Phase 2	108	LMS	Trabectedin & doxorubicin 6 cycles	Uterine 59.6%; non-uterine 55.8%	Uterine 8.2; non-uterine 12.9	Uterine 20.2; non-uterine 34.5
(D'Ambrosio et al., 2020)	Retrospective	303	LMS	Doxorubicin & dacarbazine vs. doxorubicin & ifosfamide vs. doxorubicin	30.9% vs 25.6% vs 19.5%	9.4 vs. 6.8 vs. 5.4	35.4 vs. 21.4 vs. 29.3
(Seddon et al., 2017)	Randomized, phase 3	257	STS (46% LMS)	Gemcitabine & docetaxel vs. doxorubicin	20% vs 19%	23.7 vs. 23.3 weeks	67.3 vs. 76.3 weeks
(Judson et al., 2014)	Randomized, phase 3	455	STS (25% LMS)	Doxorubicin & ifosfamide vs. doxorubicin	26% vs 14%	7.4 vs. 4.6	14.3 vs. 12.8
(Sleijfer et al., 2010)	Retrospective	1337	STS (42% LMS)	Ifosfamide & other vs doxorubicin	20.4% vs 24.7%	4.4 vs 3.5	12.4 vs 12.0
(Hensley et al., 2008a)	Phase 2	42	uLMS	Gemcitabine & docetaxel	35.8%	4.4	16
(Lorigan et al., 2007)	Randomised phase 3	326	STS (30% LMS)	Ifosfamide (3 *3 g/m^2) vs Ifosfamide (9 g/m^2) vs doxorubicin	5.5% vs 8.4% vs 11.8%	2.16 vs 3.0 vs 2.52	10.92 vs 10.92 vs 12.0
(Von Burton et al., 2006)	Phase 2	48	STS (21% LMS)	Gemcitabine	4%	2.0	6.0

activity as a monotherapy (Von Burton et al., 2006). The combination of gemcitabine with the taxane docetaxel was suggested as a possible beneficial regimen due to the synergistic mechanisms of action (Merimsky et al., 2000; Patel et al., 2001). In a phase 2 trial of first-line gemcitabine and docetaxel treatment in uterine LMS, objective responses were observed in 35.8% of patients (Hensley et al., 2008a). Out of all evaluable patients, 4.8% achieved a complete response while 31% achieved a partial response (PR) and 26.2% achieved stable disease (SD), demonstrating that the gemcitabine and docetaxel combination can lead to high response rates and complete responses in uterine LMS patients as an initial chemotherapy regimen. However, more recently a phase 3 trial compared single agent doxorubicin treatment to combined gemcitabine and docetaxel in locally advanced or metastatic STS as a first-line treatment and found that gemcitabine and docetaxel offered no improvement in OS or PFS compared to doxorubicin in any of the subtypes including LMS, and additionally leads to higher toxicity (Seddon et al., 2017). Therefore, gemcitabine and docetaxel treatment is not recommended in the first-line setting for advanced STS but instead is recommended for LMS patients, particularly uterine LMS, who have progressed on first-line treatment.

Trabectedin is a marine-derived anticancer alkaloid and has also demonstrated clinical benefit in LMS as a first-line therapy, although almost all of these trials assess the first-line efficacy of trabectedin as a combination therapy and not as a monotherapy. In a recent trial conducted by the French Sarcoma Group, it was shown that combined first-line treatment of advanced LMS with trabectedin and doxorubicin led to an increase in response rate (38% vs 13%), median PFS (12.2 vs 6.2 months) and OS (30.5 vs 24.1 months) in the combination arm versus the doxorubicin monotherapy arm, with an enhanced but manageable toxicity profile (Pautier et al., 2022). The prolonged disease control in some LMS patients receiving trabectedin could potentially be explained by the effect on DNA repair mechanisms, whereby DNA damage repair signatures have been shown to predict responses of STS patients to trabectedin (Moura et al., 2021). More research is required to evaluate if the combination of trabectedin with doxorubicin in the first-line setting is superior to doxorubicin in the first-line followed by trabectedin in the second-line (Cojocaru et al., 2022).

The first-in-class PDGFRA monoclonal antibody olaratumab was evaluated in combination with doxorubicin in the first line setting. An early phase 1b/2 clinical trial showed promising results of this combination in anthracycline naïve advanced STS patients of which 38% were LMS (Tap et al., 2016). The combination of olaratumab and doxorubicin dramatically improved median OS to 26.5 months compared to 6.6 months for doxorubicin treatment alone and this improvement was not dependent on subtype. Interestingly no significant difference in median PFS was seen (6.6 and 4.1 months respectively, $p = 0.615$). However, a later phase 3 trial with 509 STS patients, of which 46% were LMS, failed to reproduce the previous findings and showed no significant difference in median OS in LMS patients treated with combined olaratumab and doxorubicin compared to patients treated with doxorubicin alone (21.6 months and 21.9 months respectively) (Tap et al., 2020). Median PFS was also reported to be slightly lower in the combined treatment arm compared to doxorubicin monotherapy particularly in the LMS cohort (4.3 months and 6.9 months respectively), indicating that this combination does not provide additional clinical benefit in LMS (Antoniou et al., 2018).

7. Second-line and beyond treatment in advanced disease

Gemcitabine is used in advanced or metastatic LMS as a second-line chemotherapy with only modest activity when used alone (Table 2) (Patel et al., 2001). Gemcitabine displays a response rate ranging from 3.23%– 18% in sarcomas across subtypes (Merimsky et al., 2000). However, an improved overall response rate was observed in metastatic STS patients including LMS patients who received the combination of gemcitabine and docetaxel (16%) compared to gemcitabine alone (8%) (Maki et al., 2007). Additionally, median PFS was 6.2 months and 3 months for combination or monotherapy treatment respectively and median OS was also increased from 11.5 months in the monotherapy arm to 17.9 months in the combination arm, showing this regimen can lead to improved outcomes. However, combined gemcitabine and docetaxel did show an increase in toxicity. In a retrospective study of bone and soft-tissue sarcoma patients treated with a combination of gemcitabine and docetaxel, a response rate of 43% was reported. Subtypes that received benefit included LMS, angiosarcoma, malignant fibrous histiocytomas, malignant peripheral nerve sheath tumour, osteosarcoma and Ewing sarcoma (Leu et al., 2004). In a phase 2 trial assessing the activity of gemcitabine and docetaxel in unresectable LMS patients either following progression on doxorubicin or as a first-line treatment, an impressive response rate of 53% was reported, or 50% when only considering patients who had received prior doxorubicin (Hensley et al., 2002). Since this study, further phase 2 trials in the context of second-line treatment have shown responses for this combination ranging from 21% to 27% in uterine or non-uterine LMS patients (Pautier et al., 2012; Hensley et al., 2008b).

Trabectedin is used in patients who have progressed on doxorubicin or unsuited for anthracycline treatment (Demetri et al., 2016). Early phase 2 trials initially showed that trabectedin had low response rates

Table 2
A selection of clinical trials assessing systemic chemotherapies as a second or further line of treatment for advanced LMS. LMS; leiomyosarcoma, LPS; liposarcoma, mPFS; median progression-free survival, mOS; median overall survival, STS; soft-tissue sarcoma.

Reference	Type of study	N	Subtypes	Treatment	Response rate	mPFS (months)	mOS (months)
(Blay et al., 2019)	Randomised phase 3	309	LMS	Eribulin vs dacarbazine	5% vs 7%	2.2 vs 2.6	12.7 vs 13.0
(Demetri et al., 2016)	Randomized, phase 3	518	LPS and LMS (73% LMS)	Trabectedin vs. dacarbazine	9.9% vs 6.9%	4.2 vs. 1.5	12.4 vs. 12.9
(Pautier et al., 2012)	Randomised phase 2	90	LMS	Gemcitabine vs Gemcitabine & docetaxel	Uterine 19% vs 24%; non-uterine 14% vs 5%	Uterine, 5.5 vs 4.7; non-uterine, 6.3 vs 3.8	Uterine, 20 vs 23; non-uterine, 15 vs 13
(Schöffski et al., 2011)	Phase 2	128	STS (31% LMS)	Eribulin	5% (LMS specific)	Not available	Not available
(Hensley et al., 2008b)	Phase 2	51	Uterine LMS	Gemcitabine & docetaxel	27.1%	6.7	14.7
(Maki et al., 2007)	Randomised phase 2	122	STS (31% LMS)	Gemcitabine & docetaxel vs Gemcitabine	16% vs 8%	6.2 vs 3.0	17.9 vs 11.5
(Le Cesne et al., 2005)	Phase 2	104	STS (41% LMS)	Trabectedin	8.1%	3.5	9.2
(Garcia-Carbonero et al., 2004)	Phase 2	36	STS (36% LMS)	Trabectedin	8%	1.7	12.1
(Yovine et al., 2004)	Phase 2	54	STS (48% LMS)	Trabectedin	11.1%	1.9	12.8
(Hensley et al., 2002)	Phase 2	34	LMS	Gemcitabine & docetaxel	53%	5.6	17.9
(Köstler et al., 2001)	Phase 2	27	STS (22% LMS)	Docetaxel	15%	2.4	7.7
(Patel et al., 2001)	Phase 2	56	STS (48% LMS)	Gemcitabine	18%	3	13.9

(8–11.1%) as a monotherapy for advanced chemo refractory STS (Table 2) (Yovine et al., 2004; Le Cesne et al., 2005; Garcia-Carbonero et al., 2004). However, a subsequent phase 3 trial found that trabectedin treatment led to a 45% reduction in the risk of disease progression or death compared to dacarbazine for heavily pre-treated, advanced LMS or liposarcoma with a response rate of 34% and 12% in trabectedin or dacarbazine treated patients respectively (Demetri et al., 2016). Based on these studies, trabectedin is recommended as an option for LMS patients who have disease progression following doxorubicin (Gronchi et al., 2021; Le Cesne et al., 2022).

Eribulin is another chemotherapeutic agent that can be used in advanced LMS patients following disease progression on first-line treatment (Table 2) (Blay et al., 2019; Phillips et al., 2022). A phase 2 trial of advanced STS patients who had previously received up to two single drugs for advanced disease showed a response rate of 5% in the LMS cohort although 32% of LMS patients demonstrated stable disease at 12 weeks after starting eribulin treatment (Schöffski et al., 2011). A later study focussed on LMS patients who had received at least 2 prior lines of chemotherapy assessed the benefit of eribulin versus dacarbazine (Blay et al., 2019). This trial reported similar response rates between the eribulin and dacarbazine arms (5% vs 7% respectively) and also a similar median PFS (2.2 vs 2.6 months) and median OS (12.7 vs 13 months respectively) with manageable toxicity profiles.

Based on the encouraging pre-clinical observations that LMS and other STS models were sensitive to multi-target anti-angiogenic therapies, the tyrosine kinase inhibitor (TKI) pazopanib has been evaluated in a range of STS subtypes including LMS (Lee et al., 2019b). The PALETTE phase 3 trial in advanced STS patients who had previously received at least one line of anthracycline treatment prior to trial enrolment showed that pazopanib significantly improved PFS compared to a placebo (4.6 vs 1.6 months respectively) (van der Graaf et al., 2012). However, the study noted no significant difference in median OS between the two arms (12.5 vs 10.7 months). Pazopanib is therefore an option for LMS patients in second-line treatment and beyond. Phase 2 studies with other TKIs of the same class such as regorafenib and anlotinib in LMS patients have been reported with broadly similar results as pazopanib (Mir et al., 2016; Chi et al., 2018; Wilding et al., 2019).

8. Ongoing clinical trials in LMS

There are several ongoing clinical trials of interest in LMS. Lurbinectedin is an analogue of trabectedin that showed clinical activity in a subset of anthracycline-naïve LMS patients when used in combination with doxorubicin in a phase II trial (Cote et al., 2020). Based on these results, a phase 1b lead-in to a phase 2 randomised study comparing the combination of lurbinectedin and doxorubicin versus doxorubicin in LMS patients who have not received prior anthracycline or trabectedin is ongoing (Cote et al., 2022) (NCT05099666). Unesbulin is a tubulin-binding agent which has shown preclinical activity in LMS when used in combination with dacarbazine (Jernigan et al., 2021). The preliminary results of a Phase 1b study of unesbulin and dacarbazine in patients with advanced LMS (NCT03761095) showed an overall response rate of 17.2% and a disease control rate of 58.6% (Tine et al., 2022). Based on these results, a randomised, placebo-controlled phase II/III trial (SUNRISE LMS, NCT05269355) in advanced LMS is ongoing. Finally, the EORTC is conducting a randomised phase III study of surgery with or without neoadjuvant chemotherapy in high-risk retroperitoneal sarcoma (STRASS2, NCT04031677). In the LMS arm, 125 patients will be randomised to 3 cycles of neoadjuvant doxorubicin and dacarbazine or surgery alone with disease free survival as the primary endpoint. The results from these three trials are eagerly awaited.

9. Drug resistance mechanisms in LMS

The major challenges facing the use of systemic chemotherapies is the accumulation of toxicity which leads to treatment discontinuation, and the development of multi-drug resistance. Multi-drug resistance poses a significant challenge to subsequent treatment, progressively lowering the response rates in patients receiving second line or further treatment regimens (Savina et al., 2017; Comandone et al., 2017). Understanding and overcoming mechanisms of drug resistance is therefore of critical importance. Mechanisms associated with chemotherapy resistance in other cancer types includes enhanced drug efflux, DNA repair, downregulation of apoptosis, and angiogenesis (Tegze et al., 2012; Lovitt et al., 2018; Gallego et al., 2022; Garcia-Ortega et al., 2022; Vaidyanathan et al., 2016). However, many of the mechanistic studies in LMS have thus far mostly focused on drug efflux, DNA repair pathway alterations and anti-apoptotic mechanisms of chemotherapy resistance (De Graaff et al., 2016; Honoki et al., 2010; Lin et al., 2012; Martin-Broto et al., 2021).

In several cancer types, multi-drug resistance to chemotherapies has been shown to be promoted by the activation of adenosine triphosphate (ATP) binding cassette (ABC) family of efflux transporters (Muriithi et al., 2020). The multi-drug resistance-associated protein 1 (MRP1) has

been shown to actively remove doxorubicin from sarcoma cells, and an association between the degree of chemoresistance, expression of *MRP1,* and reduction of intracellular drug accumulation has been well documented in several subtypes including LMS (Martin-Broto et al., 2021). In the LMS cell line SK-UT-1, doxorubicin treatment was found to cause an upregulation of MRP1. Co-treatment with the BCR/ABL kinase inhibitor nilotinib reduced doxorubicin induced MRP1 upregulation and also inhibited the efflux function of MRP1, leading to increase intracellular accumulation of doxorubicin (Villar et al., 2012). p53 loss of function has also been shown to increase the expression of MRP1, mediating chemotherapy resistance, whereby LMS cells transfected with wild type *TP53* reduced MRP1 expression and led to an increased intracellular accumulation of doxorubicin (Zhan et al., 2001).

As doxorubicin exerts its anti-tumour effects via DNA damage, the alteration of DNA damage response and repair pathways is one of the main mechanisms implicated in chemotherapy resistance (Gallego et al., 2022; Boichuk et al., 2020). For instance, osteosarcoma cells which have acquired doxorubicin resistance in vitro showed reduced DNA damage following doxorubicin exposure compared to parental cells (Gallego et al., 2022). Additionally AKT has been suggested as a potential mediator of enhanced DNA repair in doxorubicin resistant LMS cells based on the observation that AKT inhibition is able to re-sensitise cells to doxorubicin induced DNA damage, leading to enhanced apoptosis (Boichuk et al., 2020).

Upregulation of anti-apoptotic proteins such as Bcl-2, Bcl-xL, and Bcl-w, and parallel downregulation of pro-apoptotic proteins including Bcl-2-associated X protein (BAX) and BCL2 Antagonist/Killer 1 (BAK) are also associated with doxorubicin resistance (Van Oosterwijk et al., 2012). De Graaff et al. reported that 77%, 84% and 42% of LMS show a high expression of anti-apoptotic proteins Bcl-2, Bcl-xL and Bcl-w respectively, and the use of Bcl-2 family inhibitor ABT-737 sensitised LMS cells to doxorubicin treatment (De Graaff et al., 2016). Proteomic analysis also demonstrated the upregulation of anti-apoptotic protein Bcl-w in acquired doxorubicin resistant LMS cell lines (Lin et al., 2012). Mechanistic investigation of chemoresistance showed that when LMS cells were transfected with the kinase MELK, an upregulation of Bcl-2 via the activation of the JAK-2/STAT-3 pathway induced doxorubicin resistance while the opposite effect was observed upon MELK suppression (Zhang et al., 2020). Furthermore, high MELK expression in LMS tumours also correlated with poor survival outcomes. Additionally, a recent study showed that primary STS cells including LMS with *p53* mutations, a key regulator of apoptosis, harboured doxorubicin resistance via reduced apoptotic signalling (Kirilin et al., 2022).

10. PARP inhibitors as novel agents in LMS

Deficiency in the HR pathway or BRCAness is known to confer sensitivity to DNA-double strand break inducing drugs, including platinum based derivatives and poly (ADP-ribose) polymerase (PARP) inhibitors (Helleday, 2011). Several PARP inhibitors have now been approved for use in BRCA1/2 deficient breast, ovarian, prostate and pancreatic cancers (Geenen et al., 2018; Lord and Ashworth, 2017). Olaparib was the first PARP inhibitor approved by the FDA as a treatment for advanced BRCA1/2 mutated ovarian cancers (Kaufman et al., 2015) and has now also been approved for treatment of BRCA1/2 mutant HER2-negative breast cancer and advanced pancreatic cancer (Robson et al., 2019; Golan et al., 2019). PARP inhibitors have also shown activity beyond BRCA1/2 mutant tumours, such as in cancers which show HR deficiency or mutations in DDR associated genes. Olaparib has further been approved for the treatment of recurrent ovarian cancer regardless of BRCA1/2 mutation status and recently for the treatment of HR deficient prostate cancer (Pujade-Lauraine et al., 2017; de Bono et al., 2020). Other PARP inhibitors which have been approved for treatment in various cancer types include niraparib, rucaparib and talazoparib (Litton et al., 2018; González-Martín et al., 2019; Oza et al., 2017; Coleman et al., 2017; Abida et al., 2019).

Pre-clinical reports have demonstrated that some LMS cell lines are sensitive to PARP inhibition, although these studies have been limited to a few LMS cell lines which does not capture the full range of genomic heterogeneity in this subtype. For instance, sensitivity to the PARP inhibitor niraparib was observed in the uterine LMS cell line SK-LMS-1 which has HR deficiency but does not harbour BRCA1/2 mutations, suggesting that sensitivity to this class of drugs in LMS is not limited to BRCA1/2 mutations (Li et al., 2020). Additionally, temozolomide, a DNA alkylating chemotherapeutic agent, was also shown to synergise with PARP inhibitor treatment in SK-LMS-1 when used in combination compared to doxorubicin, ifosfamide or dacarbazine (Li et al., 2020). In a separate study, the BRCA2 mutant uterine LMS cell lines SK-UT-1 and SK-UT-1b were shown to be sensitive to the PARP inhibitor olaparib in a clonogenic assay, an effect which was amplified by pre-treatment with cisplatin (Chudasama et al., 2018).

There are a number of clinical trials investigating PARP inhibitor therapies in STS patients. Early data from these studies have shown promising initial results in the context of advanced disease following failure of first-line chemotherapy, particularly in uterine LMS (Asano et al., 2022). A case series of four uterine LMS harbouring BRCA2 loss of function mutations were assessed for response to PARP inhibitor treatment. These patients had received at least four lines of treatment prior to initiation of PARP inhibitor, which led to stable disease for at least 12 months in three patients and partial response in one patient (Seligson et al., 2019). In another case series of five high-grade uterine LMS, three harbouring biallelic *BRCA2* inactivation and two with somatic or germline truncating *BRCA2* mutations accompanied with loss of heterozygosity, were treated with the PARP inhibitors in various clinical trials or off label. All five patients had a response with radiographic regression and duration of treatment ranging from 6 to 28 months. Additionally, one patient had a complete response and remained on treatment at the time of the time of the report (Hensley et al., 2020). Furthermore, a case report identified a somatic BRCA2 mutation in a patient with advanced metastatic uterine LMS, previously treated with gemcitabine and docetaxel as a first-line therapy. Treatment with olaparib led to a complete response, with the patient remaining disease free for two years at the point of publication (Shammas et al., 2022). PARP inhibitor treatment can therefore achieve durable responses in uterine LMS patients with BRCA mutations despite disease progression on previous chemotherapy (Shammas et al., 2022).

Preliminary results from a phase Ib trial utilising olaparib and concomitant radiotherapy in locally advance or unresectable STS was well tolerated with 3/22 unconfirmed partial response (14%) and 12/22 stable disease (55%) reported (Sargos et al., 2022). Another phase Ib study assessed the combination of olaparib and trabectedin in patients with advanced LMS (30%) and other STS, and bone sarcomas. This trial reported a response rate of 14% with manageable toxicity (Grignani et al., 2018). The authors also investigated biomarkers of response and found that high PARP1 expression of tumours correlated with improved outcomes. A phase 2 study evaluated the treatment of advanced uterine LMS patients with the combination of olaparib and temozolomide and reported objective response rates of 27% (6/22) which met the prespecified primary efficacy endpoint (Ingham et al., 2021). Additionally, the study reported median PFS and duration of response of 6.9 and 12 months respectively, indicating relatively durable responses. Haematological toxicity was common, with grade 3/4 neutropenia and thrombocytopenia seen in 77% and 32% of patients respectively, although this was managed with dose modification.

Multiple other trials evaluating PARP inhibitors are ongoing including a phase 2/3 trial to assess the efficacy of olaparib and temozolomide combination treatment in unresectable or advanced uterine LMS following progression on chemotherapy. This trial will compare the efficacy of this combination to standard of care second-line therapies for LMS including pazopanib and trabectedin (NCT05432791). Additionally a phase 2 trial has also recently been approved to assess niraparib monotherapy in advanced or metastatic LMS (NCT05174455).

It is clear that there is a subgroup of LMS patients that benefit from PARP inhibitors. However, in order to deliver this class of drugs effectively, mechanistic biomarkers need to be identified. Given that the frequency of deep deletions in BRCA1/2 and other HR repair genes is low in LMS, other measures of BRCAness are currently under evaluation, including the use of HR deficiency scores, genomic mutational signatures, RAD51 status and PARP1 expression levels. There is therefore a unique opportunity for the development precision medicine-based biomarker-matched therapy for LMS. International collaboration is required to undertake prospective validation of such candidate biomarkers to enable LMS patients who are most likely to benefit from PARP inhibitor therapy to receive this class of drugs.

11. Conclusion

LMS remains a challenging disease to treat, particularly in the advanced setting. Key challenges that need to be addressed include, the improvement of cure rates in localised disease by incorporating risk stratification and optimising peri-operative chemotherapy, the introduction of new targeted agents such as PARP inhibitors into the arsenal of treatment options for advanced disease and a deeper understanding of the biological basis of drug response and resistance. Underpinning these advances is our emerging knowledge of the genetic alterations that drive disease progression and evolution as well as delineating the molecular heterogeneity of this complex disease to identify new drug targets and biomarkers for patient stratification. Given the rarity of this disease, global collaboration is essential to identify better treatment options to ultimately improve survival outcomes for patients with LMS.

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