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Recent advances in understanding and managing leiomyosarcomas

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Abstract

Leiomyosarcomas are malignant mesenchymal tumours that derive from the smooth muscle lineage. They are studied and frequently treated as if they are the same as other soft tissue sarcomas. Recent developments suggest that a different approach may be more appropriate. Their underlying genetic mechanisms remain unclear, and complex. Unbalanced karyotypic defects are the only shared features observed across different leiomyosarcoma subtypes. Unlike other soft tissue sarcomas, leiomyosarcomas are particularly sensitive to the combination of gemcitabine and docetaxel. Furthermore, treatment with trabectedin has shown a good efficacy in leiomyosarcomas, mainly in the form of chronic disease stabilisation.

Introduction

Leiomyosarcoma has been classically reported as the most frequent soft tissue sarcoma subtype together with liposarcoma [1]. It is classically considered that leiomyosarcomas are tumours that originate from the smooth muscle cells, or precursor mesenchymal stem cells committed to this line of differentiation [2]. As these cells are present practically in all organs, leiomyosarcomas can arise anywhere in the body. The most common location of soft tissue leiomyosarcoma is the retroperitoneum, including the pelvis. Leiomyosarcoma is the predominant sarcoma arising from large blood vessels, most commonly the inferior vena cava, and its major tributaries [3]. Leiomyosarcomas involving non-retroperitoneal soft tissues constitute a third group. These are found most frequently in the lower extremities, accounting for 10–15% of limb sarcomas [4], but may develop elsewhere. Tumours occur at intramuscular and subcutaneous localisations in approximately equal proportions. In addition, leiomyosarcomas of the uterus, with an estimated incidence of 0.64 per 100,000 women, are among the most common uterine sarcomas, and likely account for the single largest site-specific group of leiomyosarcomas [5].

As in soft tissue sarcomas in general, the overall incidence of leiomyosarcomas increases with age, and peaks at the seventh decade. By contrast, uterine leiomyosarcoma occurs from the third decade into old age, but is more common in the perimenopausal age group, in the fifth decade [6]. The sex incidence depends on the primary tumour site, with most patients with retroperitoneal and inferior vena cava sites being women [7], whereas there is a mild male predominance in non-cutaneous soft tissue sites and cutaneous leiomyosarcomas [8].

Causes and predisposing factors

There are few clear causal or predisposing factors identified for leiomyosarcomas. Epstein-Barr virus (EBV) infection, in the setting of severe immunosuppression, has been associated with leiomyosarcomas among patients with acquired immunodeficiency syndrome (AIDS) or post kidney, cardiac, and liver transplantation [9,10]. Most cases are truly multicentric, based on independent EBV

infection rather than metastasis [11]. Other traditional risk factors for sarcomas, such as radiotherapy, rarely lead to the development of leiomyosarcomas [12], unlike the osteosarcomas or angiosarcomas. Predisposition to tumours (including, rarely, leiomyosarcomas) is found in Li-Fraumeni syndrome, which is associated with germline defects in TP53 [13]. Patients with hereditary retinoblastoma have a cumulative risk of 13.1% for developing soft tissue sarcoma as a secondary malignancy [14], including leiomyosarcomas, which further supports the relevance of RB1 loss in sporadic leiomyosarcomas (discussed later). The familial syndrome hereditary leiomyomatosis with renal cell carcinoma (HLRCC), in which there are germline mutations in fumarate hydratase, has also been associated with an increased risk of uterine leiomyosarcomas [15]. Some studies have suggested an increased risk of uterine sarcoma among women with a history of obesity and diabetes [16], and among women exposed to tamoxifen [17].

Pathology and tumour biology

Histopathology

Leiomyosarcoma is a malignant mesenchymal tumour composed of cells showing distinct features of smooth muscle lineage. The typical histological pattern of leiomyosarcomas is that of intersecting, sharply marginated fascicles of spindle cells, with characteristically elongated and blunt-ended nuclei. This pattern may be less well-differentiated in some tumours and, occasionally, there is some focal storiform, palisaded, or haemangiopericytoma-like arrangement. Nuclear hyperchromasia and pleomorphism are generally notable, although they may be focal, mild or occasionally absent. The cytoplasm varies from typically brightly eosinophilic to pale [18].

Using immunohistochemistry, smooth muscle actin, desmin and h-caldesmon are positive in a great majority (>70%) of leiomyosarcomas, also none of these markers are specific for smooth muscle differentiation [18]. When investigating by immunohistochemistry, estrogen receptors and progesterone receptors are expressed in most uterine leiomyosarcomas (in 43–57% for estrogen receptors and in 40–43% for progesterone receptors) [19,20].

In contrast to many other soft tissue tumours, the genetics of smooth muscle tumours are poorly understood and such diagnostic testing is not yet generally applicable in this histogenetic group. Karyotypes of soft tissue leiomyosarcomas are usually highly complex with genomic instability, and often associated with defects in *TP53* or sometimes *FANCA* [21] and *ATM* [22]. Frequent regions of chromosomal loss and, less frequently, gain have been reported [23,24]. The most consistent changes detected across several studies are losses in chromosomes 10q11 to 21.2 and 13q14.3 to q21.1, and gains at 17p11 to p12. Regions deleted in 10q and 13q harbour two important tumour suppressor genes: *RB1* and *PTEN*, respectively. *TP53* is mutated in about 25% of sporadic leiomyosarcomas and 50% of samples present biallelic TP53 inactivation [25]. There is frequent involvement of the retinoblastoma-cyclin D pathway with genomic loss at 13q14 centred on the *RB1* gene [26,27]. Loss at 9p21 or promoter hypermethylation results in low expression of variously spliced CDK2NA transcripts that encode ARF and inhibitors of CDK4 [28]. Analysis of several gene-expression profiling datasets suggest that there are multiple molecular subgroups of leiomyosarcomas, including a "muscle-enriched" subtype, and less differentiated groupings with indications of different frequencies of specific genomic changes and varying prognoses [21,29,30]. Interestingly, some tumours classified as undifferentiated pleomorphic sarcomas cluster closely with a subset of leiomyosarcomas, suggesting similarity and perhaps supporting the existence of "dedifferentiated" leiomyosarcomas [21,29-31]. Expression of receptor tyrosine kinase-like orphan receptor 2 (ROR2) has been shown to play a role in the invasiveness of leiomyosarcomas (gynaecological and non-gynaecological) *in vitro* and is predictive of poor clinical outcome [32].

Principles of general management: diagnosis

Clinical features

Leiomyosarcoma of the soft tissue generally presents as a mass lesion. Retroperitoneal tumours may be painful. Clinical presentation of leiomyosarcomas, as of other soft tissue sarcomas, is often associated with non-specific symptoms caused by displacement of structures, rather than invasion. The symptoms produced by leiomyosarcomas of the vena cava depend on the portion involved. For uterine leiomyosarcomas, there are neither distinctive symptoms nor pathognomonic features on any imaging technique; therefore, the diagnosis is made by histologic examination of the tumour specimen after surgery only.

Imaging studies of leiomyosarcomas are non-specific, but helpful in delineating the relationship to adjacent structures, particularly in the retroperitoneum. Usually, imaging approaches include magnetic resonance imaging (MRI) in soft tissue tumours, and contrast-enhanced computed tomography (CT) scan for retroperitoneal lesions. Chest and abdominal CT scan is required in the initial work-up, because haematogenous spread is a frequent event in leiomyosarcomas, and the lung and liver are two common sites of metastases. Leiomyosarcoma is the commonest sarcoma giving rise to metastases to the skin. Soft tissue and bone metastases are also seen [33,24].

For soft tissue, visceral and retroperitoneal sarcomas, pretreatment biopsy is mandatory. Following appropriate

imaging assessment, the standard approach to diagnosis consists of multiple core needle biopsies [34]. Biopsies should be obtained by a radiologist or surgeon after multidisciplinary discussion, as needed, within reference centres. They should be planned in such a way that the biopsy pathways and the scar can be safely removed by definitive surgery [34], and to minimize contamination and complications. The biopsy entrance can be tattooed. For retroperitoneal sarcoma, open and laparoscopic biopsies must be avoided.

Prognostic factors

In leiomyosarcomas, as in other soft tissue sarcomas, histologic grade, tumour size, and tumour depth are the three major clinicopathologic factors that establish the risk profile. They are all included in the American Joint Committee on Cancer (AJCC) staging system for soft tissue sarcomas [35]. To establish the grade, the Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading system is generally used, which distinguishes three malignancy grades based on differentiation, necrosis and mitotic rate [36]. Histological grading is an independent indicator of the degree of malignancy, probability of distant metastases, and of disease-specific survival [35,37,38], except for uterine leiomyosarcomas where the diagnosis is in itself an unfavourable prognostic factor [39]. Approximately 90% of leiomyosarcomas are reported to be moderate to high grade [35]. Leiomyosarcoma is the commonest sarcoma giving rise to metastases to the skin. Soft tissue and bone metastases are also seen [33]. Atypical intradermal smooth muscle neoplasm (formerly called cutaneous leiomyosarcoma) constitutes a distinctive entity with excellent prognosis, because it arises in the dermis and does not develop metastasis [40]. For uterine leiomyosarcomas, the revised 2008 International Federation of Gynaecology and Obstetrics (FIGO) staging system is still used to predict patient outcome [41]. Currently, the overall predictive ability of AJCC staging is not superior to FIGO staging. Thus, for the majority of women with uterine leiomyosarcomas, the currently available staging systems fail to provide a good estimate of progression-free survival (PFS) and overall survival (OS) [42].

Surgery

Surgery is the cornerstone treatment for all patients with an adult type, localised soft tissue sarcoma, and subsequently for leiomyosarcomas. The standard surgical procedure is a wide excision with negative margins (R0) 34 for soft tissue leiomyosarcomas. This implies removing the tumour with a rim of normal tissue around it. The standard treatment of primary retroperitoneal sarcoma is surgery, performed by a surgeon with specific sarcoma expertise, and it should aim to achieve macroscopically complete resection in one specimen "bloc" and minimise microscopically positive margins. This is best achieved by resecting the tumour "en bloc" with adherent structures, even if not overtly infiltrated [34]. Preservation of specific organs should be considered on an individual basis and mandates specific expertise in the disease in order to make appropriate decisions. Considering uterine sarcomas, there are currently no clinical and radiological criteria to differentiate leiomyomas from malignant tumours. Standard local treatment of uterine leiomyosarcomas, when it is localised, is abdominal total hysterectomy with bilateral salpingo-oophorectomy, although in premenopausal women a simple hysterectomy without oophorectomy can be considered. Lymph node invasion is uncommon, and lymphadenectomy has not been demonstrated to be useful when there is a lack of macroscopic involvement [34]. Nevertheless, most diagnoses of uterine leiomyosarcomas are made "a posteriori" after surgery for supposed benign uterine pathology such as leiomyoma or an endometrial polyp [43]. Procedures resulting in potential tumour cell spillage (e.g. morcellation out of endobags) are associated with a high risk of worsening the prognosis if leiomyosarcoma is the postoperative pathological diagnosis [44].

Radiotherapy

The therapeutic role of radiotherapy in soft tissue sarcoma has been shown to improve local control with preservation of the function, and to decrease local recurrence but without improvement in overall survival [45]. Thus, post-operative radiotherapy is considered to be the standard of care of nearly all intermediate-grade or high-grade leiomyosarcomas of the extremities and trunk [34,46]. For retroperitoneal sarcomas, although there is no evidence from randomized trials of neoadjuvant therapy versus resection alone, neoadjuvant therapy (chemotherapy, external beam radiation, regional hyperthermia or combinations) is safe in well-selected patients and may be considered after careful review by a multidisciplinary sarcoma tumour board. Preoperative radiotherapy in resectable retroperitoneal sarcomas is currently being investigated (NCT01344018) and preoperative treatments are intended to improve the quality of surgical margins. Postoperative adjuvant external beam radiation following complete gross resection is of limited value and is associated with significant short- and long-term toxicities [34].

In the single phase III study [47] that randomized surgically resected uterine sarcomas of grade I and II to either observation or pelvic irradiation, in which 103 patients with uterine leiomyosarcomas were included, radiotherapy demonstrated no difference in either overall survival or disease-free survival in all sarcoma subtypes. Radiotherapy demonstrated an increased local control

for carcinosarcoma patients receiving irradiation but without any benefit for leiomyosarcomas.

Systemic treatment of leiomyosarcomas

Localised disease

There is still no consensus on the current role of post-operative chemotherapy in extremity soft tissue sarcomas. Chemotherapy is not a standard treatment in adult-type soft tissue sarcoma [34]. Adjuvant chemotherapy may be proposed as an option in high-risk patients or within clinical trials [34]. Most trials evaluating adjuvant chemotherapy in sarcomas evaluate patients with high-risk soft tissue sarcomas and include many histological subtypes, making it difficult to discern a subtype-specific recommendation.

Advanced disease

Patients have a poor prognosis when leiomyosarcomas are metastatic. In prospective clinical trials, a median PFS of about 6 months and overall survival of around 12–15 months are usually reported [48] for patients treated with any first-line chemotherapy, representing a true unmet medical need. There are only two agents that have been considered active in soft tissue sarcomas in general, Doxorubicin and Ifosfamide [49,50] being the backbone of sarcoma treament. In the analyses of the large database of the European Organisation for Research and Treatment of Cancer (EORTC) on more than 2500 patients with advanced sarcomas treated with doxorubicin, and over 1700 treated with ifosfamide-based therapy, histological subtype could not be identified as an important prognostic factor of response to either doxorubicin or ifosfamide-based cytotoxic therapy, independent of other clinical factors [49,50], and no distinct histological subtype emerged as more sensitive to these agents. Nevertheless, Sleijfer *et al*. in their retrospective analysis on prognostic and predictive factors for outcome to first-line ifosfamide-based regimen in advanced/metastatic soft-tissue sarcomas reported a non-significant trend in leiomyosarcomas toward lower response-rate and lower progression-free survival compared with liposarcomas, synovialosarcomas and other sarcoma histologies [50].

Yet the analysis of 3- and 6- month progression-free survival rates after first-line drug treatment for metastatic disease from the EORTC database suggested differences in results between subtypes [51]. In addition to these data, increasing numbers of reports have suggested that the various subtypes of soft tissue sarcomas should be approached individually [52]. In the last few years, drug development in sarcomas has evolved to focus on histotype-specific trials in an effort to detect more robust and selective effects in defined soft tissue sarcoma subtypes. However, there have also been some remarkable developments in the use of chemotherapy in leiomyosarcoma.

Gemcitabine has been tested in numerous phase II studies in pretreated advanced soft tissue sarcomas that had not shown major activity (response rate of ~10%) [53–58]. Collectively, however, some activity was seen in leiomyosarcomas. The combination of a fixed-dose rate infusion of gemcitabine with docetaxel has documented activity against metastatic leiomyosarcomas, with particular emphasis in uterine leiomyosarcomas [59–62]. However, it was unclear whether this activity is due to the prolonged infusion of gemcitabine at fixed-dose rate or to synergy between the two drugs. Two multicenter randomized phase II studies addressed this question.

The SARC002 study [63] demonstrated that the gemcitabine plus docetaxel combination induced superior activity compared to a higher dose of gemcitabine, in terms of response rate (16% *versus* 8%), progression-free survival (PFS) (median PFS of 6.2 and 3.0 months in the gemcitabine plus docetaxel and gemcitabine arm, respectively), and overall survival (OS) (median OS of 17.9 and 11.5 months in the gemcitabine plus docetaxel and gemcitabine arm, respectively) in an adaptively-randomized phase II study which included all sarcoma subtypes, with broad pre-treatment characteristics from 0 to 3 prior chemotherapy regimen(s) [63]. Interestingly the response rate for patients with leiomyosarcomas was no different to other subtypes. The French Taxogem study [64], unlike the SARC002, only included patients with leiomyosarcomas after progression to a first line anthracyclin-based systemic treatment, with a stratification by site of origin (uterine *versus* non-uterine), with additional differences in gemcitabine delivery and drug intensity in the gemcitabine arm. The dose intensity of gemcitabine was very comparable between the two randomized phase II studies, although the schedules of drug administration were different.

By contrast, results from the French study [64] differed from previous data and only confirmed the benefit of the combination in terms of response rate in uterine leiomyosarcomas, not in those of non-uterine origin (in which the combination seemed to be detrimental), questioning the utility of the combination. Interestingly, median PFS was 6.3 and 3.4 months in the gemcitabine and the gemcitabine plus docetaxel arm, respectively, for non-uterine leiomyosarcomas, and 5.5 and 4.7 months in the gemcitabine and the gemcitabine plus docetaxel arm, respectively, for uterine leiomyosarcomas [64].

Another gemcitabine-based combination has shown benefit in soft tissue sarcomas, and interesting activity

in leiomyosarcomas. Garcia-Muro *et al.* [65] explored the feasibility and activity of fixed-dose rate gemcitabine plus dacarbazine in a phase II randomized trial. The combination was superior to single-agent dacarbazine, and histology showed that patients with leiomyosarcomas of any origin benefited significantly from the combination, achieving a median PFS and OS of 4.9 and 13.8 months, respectively, *versus* 2.1 and 7.8 months, respectively, for non-leiomyosarcoma subtypes.

Trabectedin (ecteinascidin or ET743) has demonstrated activity in soft tissue sarcomas with a response rate of approximately 10% in patients pre-treated with doxorubicin and ifosfamide in all histological subtypes confounded, but demonstrated a high rate of disease control more particularly on pretreated leiomyosarcomas (with 26–30% of patients progression-free at 6 months) [66–68]. Recently, a large worldwide expanded access program showed a median OS of 16.2 months in 321 heavily pre-treated leiomyosarcoma patients [69]. Trabectedin was approved by the European Medicines Agency (EMA) in 2007, and is currently available in Europe and in some other countries, but not yet in the US and Australia. A US randomized phase III trial comparing trabectedin with dacarbazine in patients with advanced leiomyosarcomas and liposarcomas has completed recruitment, and the final results are pending (NCT01343277).

Pazopanib, an oral kinase inhibitor targeting VEGF-R, PDGF-R and c-KIT, showed promising activity in a large multi-arm phase II trial of soft tissue sarcoma conducted by the EORTC [70], which was stratified by histological subtype. Activity, defined as PFS rate at 12 weeks, was seen in three sarcoma subtypes (synovialosarcomas, leiomyosarcomas and other sarcomas), but not in the adipocytic group. These results provided the rationale to conduct an international randomized phase III trial (PALETTE study) in patients with soft tissue sarcomas refractory to conventional chemotherapy (up to 4 lines of previous chemotherapy). Patients were randomized to pazopanib or placebo [71]. Although the primary end-point of the study, OS was not found to be statistically significant on an interim analysis, although there was a significant improvement in PFS (4.6 versus 1.5 months, hazard ratio: 0.31) for patients treated with pazopanib. Based on these results, pazopanib has been granted US Food and Drug Administration and EMA approval for the treatment of patients with metastatic soft tissue who have received prior chemotherapy.

Abbreviations

AJCC, American Joint Committee on Cancer; CT, computed tomography; EBV, Epstein-Barr virus; EMA, European Medicines Agency; EORTC, European Organisation for Research and Treatment of Cancer; FIGO, International Federation of Gynecology and Obstetrics; FNCLCC, Federation Nationale des Centres de Lutte Contre le Cancer; HLRCC, hereditary leiomyomatosis with renal cell carcinoma; OS, overall survival; PFS, progression-free survival.

Disclosures

The authors declare that they have no disclosures.

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