Commentary

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# Leiomyosarcoma: Principles of management

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**Summary** **The term soft-tissue sarcomas (STS) embraces more than 50 different sub-types that are often associated with poor prognosis. Only a very limited number of agents are active against STS. Doxorubicin and ifosfamide are widely accepted as the most effective compounds. However, their low response rates and poor impact on the overall survival of the patients illustrate the need for new treatment options. Among them, leiomyosarcomas are one of the most frequently occurring subtypes. In spite of the relatively high incidence of leiomyosarcomas, the overall effectiveness of the currently available systemic treatments is still poor. The heterogeneity of its biological origin, clinical behavior and responsiveness to chemotherapy, together with the scarcity of successful clinical trials, makes the treatment of leiomyosarcoma especially challenging. In addition, the evidence-based treatment for leiomyosarcoma comes from trials in which, in the majority of cases, no distinctions have been made among the different STS sub-types. As a result, every therapeutic decision should be made on an individual basis in collaboration with the patient. The results of new specific histology-designed clinical trials should aid decision making in this complex field.**

***Keywords:*** Leiomyosarcoma, sarcoma, targeted therapies, chemotherapy, hormone treatment

Soft-tissue sarcomas (STS) are a heterogeneous group of malignancies characterized by both their relatively low incidence and their poor prognosis. Classically, they have been treated as a single disease with rather disappointing results in the advanced setting. Thus, in spite of the wide range of systemic therapies available in oncology, only a very limited number of agents are active against sarcomas. Doxorubicin and ifosfamide are widely accepted as the most effective compounds. However, their low response rates (*1,2*) and poor impact on the overall survival of the patients (*3*) illustrate the need for new treatment options.

Leiomyosarcoma is one of the most frequent STS histologies with well-defined characteristics (*4*). It has been classically reported as the most frequent sarcoma sub-type together with liposarcoma (*5*). This high incidence might be due to the fact that, under the common label of leiomyosarcoma, there are a number of malignancies that differ in their biological behavior and, subsequent response to treatment. It is classically considered that leiomyosarcomas are tumors that originate from the smooth muscle cells, or precursor mesenchymal stem cells committed to this line of differentiation (*6*). As these cells are present practically in all organs, leiomyosarcomas can arise anywhere in the body. Indeed, their different behavior and sensitivity to treatment is often influenced by the site of origin. Although this observation is not exclusively confirmed in the literature (*7*), uterine leiomyosarcomas seem to be more sensitive to chemotherapy than those which arise in the vessels but vary among themselves in terms of grade and aggressiveness (*8*).

Within this broad spectrum of different origins and clinical features we can perceive distinct malignancies probably driven by different molecular alterations (*9*). However, the evidence-based treatment for leiomyosarcoma comes from trials in which, in the majority of cases, no distinctions have been made among the different sub-types.

Fortunately, the increasingly accepted change in the paradigm of the treatment of STS makes the future more promising. Thus, increasing knowledge of their molecular characterization has helped us in understanding that "STS" can no longer be considered

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as a single disease. For instance, there are sarcomas whose malignant behavior is clearly related to specific chromosomal translocations that lead to aberrant chimeric proteins. Others have complex karyotypes where the driver or drivers is unknown, whereas in other diseases, such as GIST, a specific gene mutation is responsible for driving the uncontrolled growth and resistance to death of the neoplastic cells (*10*). Together with this molecular heterogeneity, their intrinsic low incidence is an added difficulty. In order to enroll a sufficient number of patients to reach statistically significant results, the classical design of the trials allowed a broad spectrum of different histologies. Leiomyosarcomas have always been very well represented in these studies but the lack of stratification has led to results that are difficult to interpret. Some trials have even been reported as negative when the treatment assessed might have efficacy in certain subtypes. However, the clinical trials developed in the last few years have attempted to minimize these problems. Therefore, the increasing tendency is to focus on a specific sub-type or sub-types of sarcoma and also to use different statistical approaches. For instance, the EORTC in 2002 proposed new criteria of efficacy in sarcoma phase II trials in an attempt to reach achievable endpoints, with the emphasis on progression-free rates (*11*). The results of these new clinical trials began to be reported recently and, hopefully, more data will be available in the near future.

Probably for the same reasons as with cytotoxic drugs, the new targeted therapies have not achieved significant results so far. The lack of a specific target has been a handicap in the development of effective targeted drugs for the majority of solid tumors, including sarcomas. A family of targeted agents that has been widely assessed has been the multi-targeted tyrosine kinase inhibitors, perhaps principally inhibitors of VEGFR. However, few have achieved encouraging results as monotherapy. The only successful trial for advanced disease published to date (the PALETTE study, with pazopanib) did not demonstrate significant activity specifically in leiomyosarcoma patients and the overall results, although positive, are still limited (*12*). The strategy of combined treatment with targeted agents and classic cytotoxic drugs is an alternative approach, worthy of exploration. Most of the new targeted compounds recently developed in oncology produce an arrest or a slowdown in the growth of tumor cells but they may not cause cell death. Based on that premise, the rationale for combining these with cytotoxic drugs, that do effectively produce cell death, is very sensible. However, the main concern of this approach is toxicity and, unfortunately, this issue has already been proved to be potentially relevant in STS as was shown in a study by D'Adamo *et al* (*13*). New trials such as the one Gynecologic Oncology Group is currently conducting (with gemcitabine plus docetaxel plus bevacizumab in patients with advanced or recurrent uterine leiomyosarcoma) are necessary to determine whether this combined strategy is both feasible and safe.

Hormone therapy is also, conceptually, an attractive alternative for hormone-receptor positive leiomyosarcomas. Nevertheless, there are no randomized trials to date to help define the role of this treatment. Unlike endometrial stromal sarcomas, the only data available in leiomyosarcomas are just from small case series (*14-17*). The limited evidence that can be extracted from these suggests that hormone therapy might be a sensible strategy in the advanced setting for ER/PgR positive tumors with indolent growth. Otherwise, chemotherapy should be the treatment of choice.

With all these data, and considering the relative lack of evidence for the optimal treatment of leiomyosarcoma, every therapeutic decision should be made on an individual basis. For instance, adjuvant treatment may be considered in patients with a high-risk of recurrence, even though there are no randomized trial data that support it. The criteria indicative of increased likelihood of relapse for abdominal leiomyosarcomas (mostly uterine) such as tumor rupture during surgery or serosal breach are sufficient indicators of poor prognosis that adjuvant treatment may be justified. The choice of the appropriate regimen should take into consideration features like the special responsiveness that uterine leiomyosarcomas seem to have to gemcitabine and docetaxel. On the other hand, vascular leiomyosarcomas like the ones that arise from the inferior vena cava are generally considered to be particularly chemo-resistant so the real value of post-operative chemotherapy is unclear. The option of adjuvant hormone therapy might be sensible if the tumor is hormone-receptor positive, the risk of recurrence is high and the patient is not keen or is not fit enough to receive the standard chemotherapy. Also in the advanced setting, some special characteristics of leiomyosarcomas could determine the therapeutic strategy. These tumours have historically been shown to be not very sensitive to ifosfamide, so probably this drug should not be considered as the first line of treatment (*18*). As in the adjuvant setting, the special effectiveness of gemcitabine and docetaxel in gynaecological leiomyosarcomas makes it a valid option as frontline treatment instead of anthracyclines although results of direct comparison between the two regimens have not yet been reported.

In conclusion, individualized treatment must be the standard of care in a malignancy with such limited therapeutic options as leiomyosarcoma. This lack of very effective treatment makes it strongly advisable that patients should be enrolled in suitable clinical trials with new therapeutic strategies.

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