Uterine sarcomas: a multidisciplinary challenge

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With an incidence lower than 1/100,000/year, uterine sarcomas are a rare subgroup within the rare family of sarcomas, giving rise to 1% of female malignancies. However, they are a variegated set of malignancies, encompassing leiomyosarcomas, endometrial stromal sarcomas, undifferentiated endometrial sarcomas and adenosarcomas [1]. Another group, malignant mixed mesodermal tumours, are currently regarded as metaplastic (aggressive) endometrial carcinomas, i.e. epithelial tumours in nature, not sarcomas [2]. Both the low incidence and the heterogeneity of uterine sarcomas pose their first multidisciplinary challenge, inasmuch as a correct pathological diagnosis is crucial to proper management. Even the differential diagnosis between benign and malignant tumours can be problematic. One may recall the existence of a distinct entity among smooth muscle tumours, i.e. smooth muscle tumours of uncertain malignant potential (STUMP), whose behaviour is by definition unpredictable pathologically, and of benign metastasising leiomyoma and disseminated peritoneal leiomyomatosis, i.e. benign smooth muscle tumours presenting with metastatic dissemination [3]. Improvements in the pathological classification, and grading systems, for all these tumours are highly necessary.

Endometrial stromal sarcomas are low-grade malignancies, although the relapse rate after surgery of localised disease is relatively high, possibly amounting to one third of cases, although over a long period. Pathologically, these tumours are marked by their positivity for oestrogen and progesterone receptors. This underlies the efficacy in the advanced disease setting of progestins, aromatase inhibitors and gondadotropin-releasing hormone analogues [4]. Responses are frequent and long-lasting, also owing to the natural history of these tumours, even when metastatic. For this reason, surgery of lung metastases is an option to consider within a multidisciplinary approach. The usefulness of adjuvant hormonal therapies is still an open issue, given the relapse rate and the hormonal sensitivity of these tumours [5]. Bilateral oophorectomy, in addition to total abdominal hysterectomy for local treatment, also has an adjuvant intent.

Currently, endometrial stromal sarcomas are conceptually separated from undifferentiated endometrial sarcomas, although a de-differentiation process of some endometrial stromal sarcomas into high-grade sarcomas may occasionally take place [6]. Undifferentiated endometrial sarcomas are inherently high-grade malignancies (pathologically marked by a high mitotic rate, cellular pleomorphism and necrosis), which are insensitive to hormonal therapy and clinically aggressive. This considered, an aggressive, multidisciplinary approach to this rare entity is logical. Medical therapy must resort to standard agents for high-grade soft-tissue sarcomas.

On the contrary, adenosarcomas are low-grade malignancies encompassing a benign epithelial component and a low-malignant mesenchymal one. Their good prognosis is unfavourably affected when a truly sarcomatous overgrowth or myometrial invasion is present [7].

Uterine leiomyosarcomas are cured in less than one half of cases by total abdominal hysterectomy, with size and pelvic extent as the main prognostic factors. Improvements in grading systems would be required, in order to refine the prognostic value of pathological assessment. Radiation therapy did not add to surgery alone in a large randomised trial [8], in spite of positive evidence provided by uncontrolled and retrospective studies as far as the local regional relapse rate is concerned [9]. This may leave room for individualised decision-making on radiation therapy in some cases, depending on the surgical outcome and anatomical considerations. Of course, radiation therapy can be useful in local regional relapses. The efficacy of adjuvant chemotherapy is an open issue in soft-tissue sarcomas, and therefore in uterine leiomyosarcomas as well. These are essentially insensitive to hormonal therapies, although hormonal receptors are found in the tumour tissue in a proportion of cases and there is anecdotal evidence of hormonal sensitivity in occasional patients. Medical therapy in the advanced disease resorts to agents active in

leiomyosarcomas, i.e. doxorubicin and dacarbazine, gemcitabine and trabectedin [10]. These drugs can be used in a stepwise manner, as needed by the clinical evolution. The benefit of combining gemcitabine with docetaxel was suggested by one randomised Phase 2 study and denied by another. On the other hand, gemcitabine is very well tolerated as a single agent, and definitely active, as is the case with trabectedin. Both can be administered for long periods, though the usefulness of "maintaining" best tumour response is unknown. With both agents, indeed, the patient can be rechallenged if the drug was stopped after a while in the absence of progression. New agents for soft-tissue sarcomas are actively sought, and indeed the first targeted therapies (e.g. pazopanib) have shown promising results in this family of tumours as well. When selected, adjuvant treatment is currently based on doxorubicin ± dacarbazine, or gemcitabine ± docetaxel.

In brief, the prognosis of these tumours is still marked by a high relapse rate, even in early-stage presentations, and limited effectiveness of medical therapy. However, it may be improved in the individual patient by fully exploiting all available treatment modalities, while considering the variety of pathological and clinical factors that underlie the complexity of uterine sarcomas. With regard to medical therapy decisions, it is clear that data need to be extrapolated from studies in soft-tissue sarcomas in general. This may well apply to the value of adjuvant medical therapies in soft-tissue sarcomas and the anti-tumour activity of cytotoxics and targeted therapies in leiomyosarcomas. Likewise, under a multidisciplinary perspective, one can resort to information available about surgery of lung metastases in soft-tissue sarcomas, and the integrated approaches to advanced local regional sarcomas. As in sarcomas in general, the variety of clinical presentations often requires an individualised approach exploiting all available resources, including surgery of relapsing disease, radiation therapy and medical treatments. A refinement in the pathological definition of these tumours would help, especially in avoiding prognostic uncertainty and helping to select patients amenable to adjuvant treatments in the early stages.

Conflict of interest statement

For the last few years, P.G. Casali has had a consultancy/advisory role with Bayer, Merck SD, Glaxo SK, Infinity, Novartis, Pfizer, PharmaMar, Sanofi Aventis. This author received honoraria for lectures from Bayer, Novartis and Pfizer. The author received travel expenses for medical meetings from Novartis and PharmaMar. The author has been involved in clinical research sponsored by Amgen Dompé, Merck SD, Glaxo SD, Infinity, Lilly, Novartis, Pfizer, PharmaMar, Sanofi Aventis and Schering Plough.

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References

1 Amant F, Coosemans A, Debiec-Rychter M, Timmerman D, Vergote I. Clinical management of uterine sarcomas. *Lancet Oncol* 2009;**10**:1188–98.
2 Lopez-Garcia MA, Palacios J. Pathologic and molecular features of uterine carcinosarcomas. *Semin Diagn Pathol* 2010;**27**:274–8.
3 D'Angelo E, Prat J. Uterine sarcomas: a review. *Gynecol Oncol* 2010;**116**:131–9.
4 Reicha O., Regaue S. Hormonal therapy of endometrial stromal sarcoma. *Curr Opin Oncol* 2007;**19**:347–52.
5 Malouf GG, Duclos J, Rey A, et al. Impact of adjuvant treatment modalities on the management of patients with stages I–II endometrial stromal sarcoma. *Ann Oncol* 2010;**21**:2102–6.
6 Bartosch C, Exposito MI, Lopes JM. Low-grade endometrial stromal sarcoma and undifferentiated endometrial sarcoma: a comparative analysis emphasizing the importance of distinguishing between these two groups. *Int J Surg Pathol* 2010;**18**:286–91.
7 Arend R, Bagaria M, Lewin SN, et al. Long-term outcome and natural history of uterine adenosarcomas. *Gynecol Oncol* 2010;**119**:305–8.
8 Reed NS, Mangioni C, Malmström H, et al. Phase III randomised study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I and II: an European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group study (protocol 55874). *Eur J Cancer* 2008;**44**:808–18.
9 Sampath S, Schultheiss TE, Ryu JK, Wong JY. The role of adjuvant radiation in uterine sarcomas. *Int J Radiat Oncol Biol Phys* 2010;**76**:728–34.
10 O'Cearbhaill R, Hensley ML. Optimal management of uterine leiomyosarcoma. *Expert Rev Anticancer Ther* 2010;**10**:153–69.