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European Journal of Cancer's Biennial report on soft tissue and visceral sarcomas or the rapid evolution of treatment concepts in sarcomas

Jean-Yves Blay*, Mehdi Brahmi, Isabelle Ray-Coquard

Department of Medical Oncology, Centre Leon Berard, 28, rue Laennec 69008, Lyon, France

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Abstract Soft tissue and visceral sarcoma gather a large group of rare to very rare cancers and locally aggressive connective tissue tumours. Novel concepts on histological and molecular classification, optimal management of patients, systemic adjuvant and neoadjuvant treatment have been emerging in the last 5 years. In the present publication, we review and summarise significant changes which impact on disease management in this group of rare cancers.

Soft tissue and visceral sarcomas are rare adult cancers, with an incidence <6/100,000/year, gathering over 80 histological subtypes and even more molecular subtypes. While rare, sarcomas have often represented paradigmatic models in oncology for a number of topics, from multidisciplinary therapeutic management in rare cancers, to molecular characterization used to guide targeted therapeutics. We summarise here recent results which impact significantly on our vision of this disease.

1. Centralised histological and molecular diagnosis in reference centres

Because of their rarity, and also of evolving classifications over years, sarcomas have always been considered as complex diagnoses, often requiring centralised secondary opinion by expert pathologists [1,2]. Histological grading is now standardised but may be completed in the future by molecular grading such as the complexity

* *Corresponding author.*
E-mail address: jean-yves.blay@lyon.unicancer.fr (J.-Y. Blay).

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index in sarcoma (CINSARC) molecular grading, based on an analysis of genomic instability of tumour cells [1]. Indeed, the characterization of molecular alterations has further complexified the classification of sarcomas, adding as an additional dimension to histology. The nature of the main molecular alteration ('driver') now often contributes to define a nosological entity; as examples, we can quote 1) sarcomas with translocations (e.g. synovial sarcomas), 2) with kinase mutations (e.g. gastri intestinal stromal tumors (GIST)), 3) with chromosome 12q13–15 amplification (e.g. well differentiated/dedifferentiated (WD/DD) liposarcoma), 4) with tumour suppressor gene loss (e.g. malignant peripheral nerve sheath tumors (MPNST) with NF1 deletions), and 5) sarcoma with complex genomic rearrangements (e.g. undifferentiated pleomorphic sarcoma (UPS), leiomyosarcoma (LMS)). Locally aggressive connective tissue tumours with no or low risk of metastases, such as giant cell tumours of the bone, or giant cell tumour of the soft tissues (TCGT), aggressive fibromatosis are diagnosed most often by the same teams, and also exhibit characteristic genomic alterations, such as translocations, or point mutations in histones (H3.3A), or signalling proteins (beta catenin). In recent publications, molecular diagnoses were found necessary to guide the management of these tumours in over 20% of the cases [3]. Importantly also, the diagnosis of sarcoma was demonstrated to be improved when a second review is performed by an organised referral system of expert centres [2]. In an exhaustive epidemiological series collected in 3 different European regions, it was shown that second opinion for pathology modified the final diagnosis in over 30% of the cases, with major modifications in diagnosis (e.g. benign to malignant, carcinoma to sarcoma) in close to 10% of the cases [2]. A major challenge will be to implement broadly these services, at a time where the histological and molecular diagnosis is becoming crucial to define the optimal therapeutic strategy.

2. Local treatment by reference centres

A biopsy performed by an expert radiologist or surgeon, ideally after a multidisciplinary team discussion is the first step of the therapeutic strategy. Primary removal of a soft tissue mass without diagnosis should be discouraged, and all soft tissue tumours above 5 cm should be biopsied first. Local treatment is the essential step of the curative treatment of sarcoma, and surgery with en-bloc resection, performed by an experience surgeon, is the mainstay of treatment. A macroscopically complete resection with histologically negative margins (R0) is the goal; when tumour cells are found on resection margins (R1 resection), the risk of relapse increases substantially with hazard ratios between 2 and 3 in most series; relapses occur in >90% when tumour resection is macroscopically incomplete (R2 resection); an inappropriate surgery cannot be compensated by a subsequent adjuvant treatment [1,2]. In a population-based study of over 800 patients with sarcoma diagnosed during 2 years in a region of 5.9 million inhabitants, surgery performed outside of an expert reference centre was associated with an absolute decrease of 20% for progression free survival (PFS) at 5 years, with a hazard ratio of 2.27 [4]. Importantly, overall survival was significantly worse even in non-reference centres for R0 resections [4]. The quality of surgery and the expertise of the team influences prognosis more than any other treatment. As proposed now in several countries, the management of sarcoma patients should be performed in network of reference centres [5].

3. Systemic treatment in localised phase

Adjuvant or neoadjuvant radiotherapy is recommended for all deep seated, high-grade limb sarcomas. Conversely the role of adjuvant chemotherapy remains unclear [1]. Reductions in the risk of local and metastatic relapses were reported in a meta-analysis published in 1997, but more recent studies provided inconsistent results on the impact of adjuvant chemotherapy in grade II or III sarcomas. Patients benefiting from adjuvant chemotherapy remain therefore poorly defined, and clinical practice guidelines (CPGs) do not provide straightforward recommendation. A recent meta-analysis of the 2 European Organisation for Research and Treatment of Cancer (EORTC) trials provided important information on this question: patients who had R1 resections, male patients and patient aged >40 derived most benefit from adjuvant CT in these trials [6]; other works have identified grade III, and large tumours as critical predictive parameters for selection of adjuvant chemotherapy. Additional trials performed in selected histological and molecular subtypes are needed to conclude on the utility of adjuvant chemotherapy in these patients. While the most recent adjuvant trials took more than decades to complete accrual, recent data on neoadjuvant chemotherapy in limb sarcoma obtained from a randomised clinical trial comparing a standard epidoxorubicin/ifosfamide regimen [7], to histology-adapted regimens (NCT01710176) may promote the use of neoadjuvant chemotherapy (CT) as a standard approach for localised sarcoma management in the near future (Gronchi *et al.*, ESMO 2016 submitted).

4. Cytotoxic and targeted treatments in advanced phase

A recent series of negative randomised phase III clinical trials have been reported for the first-line treatment of advanced soft tissue sarcoma. While the combination of optimal doses of ifosfamide and doxorubicin significantly improved PFS in advanced sarcoma patients aged