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2018 ESMO Sarcoma and GIST Symposium: 'take-home messages' in soft tissue sarcoma

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ABSTRACT

The 7th edition of the 'ESMO Sarcoma and GIST Symposium' was held in Milan in February 2018. For the first time, the Symposium brought together representatives from the European Reference Network on rare adult solid cancer (EURACAN) joined by sarcoma experts from the USA, Japan and patient advocacy groups, to share insights and discuss future directions in this rare condition. This commentary will summarise the highlights in soft tissue sarcomas.

INTRODUCTION

The 7th edition of the currently named 'ESMO Sarcoma and GIST Symposium' was held in Milan in February 2018. So far, the symposium has taken place every 2 years and focuses on soft tissue sarcomas (STSs) and gastrointestinal stromal tumours (GIST), a group of rare cancers accounting for less than 1% of all adult solid neoplasms. For the first time, the 2018 event was held when EURACAN, the European Reference Network (ERN) on rare adult solid cancers (http://euracan.ern-net.eu) was in place. EURACAN is a network of 66 reference centres in rare cancers selected by national governments within the EU. By bringing together the main stakeholders in rare cancers, EURACAN aims to improve the quality of care, first of all through consensus-based clinical practice guidelines, share best practice, disseminate patient information and medical education and foster research. In the context of this new European scenario, the '2018 ESMO Sarcoma and GIST symposium' brought together nearly 500 participants from Europe, USA and Asia, including EURACAN representatives, sarcoma experts, researchers and patients, providing a forum for the sarcoma community to discuss state-of-the-art treatments and how to move forward in this rare condition. This commentary will summarise the highlights in STSs.

MANAGEMENT OF LOCALISED DISEASE

Extremity soft tissue sarcoma

Surgery is the standard treatment for extremity soft tissue sarcoma (ESTS). Adequate resection entails negative margins, the definition of which is not trivial. Sarcomas occur in the connective tissues and the tumour capsule may be part of the tumour. Hence the definition of negative margins depends on healthy tissue surrounding tumour surface. A soft tissue tumour should be excised completely encircled with its surrounding tissues. In this regard, there are natural barriers that often resist to sarcoma infiltration, such as muscle fascia, the joint capsules, the adventitia, the epineurium and the periosteum. If intact, they protect against tumour spreading. Once these barriers are invaded by tumour, the management of major vessels and nerves, as well as bone and joints is weighted in the context of disease biology and function preservation. There is evidence suggesting that preplanned positive margins are associated with a better outcome in terms of local relapse (LR) free-survival and cause specific survival compared with unexpected positive margins. This is particularly true if planned close dissection was performed to preserve critical structures (outcome is similar to resection with negative margins).[1] These results point to the importance of considering disease biology when planning surgery. Along the same lines, the consequence of positive margins differs by histology. In low-grade well-differentiated liposarcoma, positive margins do not increase LR rates whereas in myxofibrosarcoma, which has a high risk of LR, inadvertent positive margins significantly increase it.[2–4]

Radiotherapy and chemotherapy may offset the negative prognostic impact of positive surgical margins, but their impact varies widely among histological subtypes. In two randomised controlled trials, radiotherapy decreased LR rates with no effect on overall survival (OS).[5] Radiotherapy is a standard treatment for high-risk deep lesions. During the meeting, R. Haas presented several large retrospective series, which raised the possibility that radiotherapy may also improve

OS, but concluded that high-level evidence is lacking. B. Catton described the caveats regarding the timing of radiotherapy. While neoadjuvant radiotherapy resulted in higher wound complications, it had better long-term functional outcomes. In addition, a postoperative boost of radiotherapy can be omitted in the neoadjuvant setting. Due to the complexity of decision-making in the management of ESTS, patients should be referred to specialised centres.

Retroperitoneal sarcoma

Surgery is the cornerstone of treatment for retroperitoneal sarcoma (RPS). Primary surgery with clear margins improves outcomes and should be performed in a specialised sarcoma centre.[6] However, tumour location and size limit the application of commonly used definitions of clear margins. During the symposium, C. Swallow showed that R1 rates differ between institutions and rely on subjective pathological evaluation. Moreover, the clinical significance of R1 has not been substantiated by research. Hence R0 and R1 should be grouped together prognostically. The value of R2 resection is questionable apart from palliative indications.[6] Adequate surgery for RPS should be defined as macroscopically negative. Similar to ESTS, histology is important in RPS. A. Gronchi proposed a histology-driven choice of surgical margins, aggressively seeking R0 resections in diseases with a high risk of LR (such as liposarcoma), and a more conservative approach in diseases with a high risk of systemic recurrence (such as leiomyosarcoma). Of note, in solitary fibrous tissue (SFT), resection of the tumour mass with minimal margins is sufficient. These differences in the surgical management of RPS imply the need for a preoperative biopsy to plan the procedure.[7]

The difficulty of achieving a margin-free resection and the desire to improve long-term outcomes make multimodal neoadjuvant treatment an attractive option.[8] The effectiveness of radiotherapy has been reported in retrospective and non-controlled studies, which also found an increase in toxicity.[9] E. Baldini argued that until the STRASS study (NCT01344018) is published, evidence for the use of radiotherapy to decrease LR in RPS remains extrapolated from extremity STS. A preliminary report from the STRASS study showed that radiotherapy is safe, even when combined with extended surgery.[9] The use of chemotherapy in the neoadjuvant setting may downsize the tumour, improve local control rates and treat systemic micrometastatic disease. In addition, CT may also act as radiosensitiser if combined with RT. A phase I trial has shown that preoperative radiochemotherapy is feasible.[10] However, there is no evidence that it is more effective than surgery alone. Histology may help exclude chemoresistant patients. Further research on the neoadjuvant approach should focus on the relatively chemosensitive histological subtypes, such as leiomyosarcomas, undifferentiated pleomorphic sarcomas and high-grade dedifferentiated liposarcomas. The preoperative use of drugs recently approved in the metastatic setting might widen therapeutic armamentarium.

MANAGEMENT OF ADVANCED DISEASE

Metastatic disease develops in approximately 50% of patients with STS and is associated with poor prognosis. Across and within STS subtypes, metastatic disease exhibits a wide diversity of natural history and treatment sensitivity, reflecting a biological heterogeneity that is incompletely understood.

The lungs are the main site of metastatic spread, although the pattern of recurrence varies according to the histological subtype and may include the soft tissue, bone, liver and even brain. P. Hohenberger provided the audience with an update on current practice and evidence relating to the resection of metachronous lung metastasis in patients without extrapulmonary disease. While evidence of the survival benefit of metastasectomy remains hard to formally prove, careful consideration of patient and disease-specific factors should inform the selection of patients for surgery. Factors such as a disease-free interval of more than 1–2 years and no lesion diameter exceeding 2–3 cm were associated with improved OS in a large retrospective review.[11]

Patients with synchronous and/or extrapulmonary metastases should be considered for systemic therapy. S. Patel reviewed the current standards of care, noting the importance of considering patient-specific goals of therapy and potential predictors of effect when sequencing and selecting therapies from the broad range of available agents. For example, the increased rate of objective response and improved progression-free survival (PFS), but not OS, seen with combination doxorubicin-ifosfamide compared with doxorubicin single agent seen in a phase III trial suggests that the combination regime may be optimally employed in more chemosensitive histotypes or when tumour shrinkage is a specific goal.[12] Meanwhile, the recent provisional approval of the anti-PDGFRα monoclonal antibody olaratumab in combination with doxorubicin, based on randomised, open-label phase II evidence of a dramatic improvement in OS compared with doxorubicin single agent, indicates a potential first-line option that may confer a survival advantage, but the absence of incremental gain in response rate (RR) or PFS needs to be considered.[13]

P.G. Casali outlined the evidence for histology-driven chemotherapy in advanced STS. The challenges of heterogeneity, clinical trial methodology and utility of surrogate efficacy endpoints were discussed as well as the potential applicability and integration of both prospective clinical trial data and retrospective case series and reports. The approval of the multitarget tyrosine kinase inhibitor pazopanib in non-adipocytic STS, and the cytotoxic agents eribulin in liposarcoma and trabectedin in L-sarcomas, respectively, reflect the improved potential of phase III studies that preselect potentially sensitive trial populations based on preclinical and early phase trial data.[14–17] Additionally, P.G. Casali highlighted the valuable information that non-comparative phase II studies have provided for identifying STS subtypes with apparent drug-specific sensitivities, such as high-dose

continuous ifosfamide in dedifferentiated liposarcoma and synovial sarcoma. This approach reflects an ongoing movement towards histology-driven selection of treatment while correlations with molecular biology across histologies are weak.

Special entities and rare sarcomas

There is consensus in the sarcoma community that a histology-tailored approach should be used in several rare STS subtypes and this has also been incorporated in the recently updated joint ESMO/EURACAN Clinical Practice Guidelines.[18] Multiple examples in the choice of systemic treatments were highlighted at the meeting, such as the peculiar activity of taxanes and gemcitabine in angiosarcoma and m-TOR inhibitors in malignant perivascular epithelioid cell tumours (PEComas), which are often associated with a disruption in the m-TOR pathway.[19–21] Given the low incidence of these entities, the evidence for treatment is rarely from controlled studies and thus there is a greater degree of formal uncertainty. As outlined in the talk by S. Stacchiotti, solid preclinical data could be viewed as reducing uncertainty though in the face of limited direct evidence, and the example of imatinib in dermatofibrosarcoma protuberans (DFSP) was discussed. DFSP is an STS subtype in the skin with a translocation, t(17;22)(q22;q13), that leads to the fusion of collagen type 1α1 (*COL1A1*) and platelet-derived growth factor B (*PDGFB*). The strong preclinical rationale together with prospective uncontrolled data on imatinib activity in this subtype supported the activity and efficacy of imatinib in this disease from the beginning and had regulatory implications.[22] A similar scenario exists for crizotinib, an anaplastic lymphoma kinase (ALK) and MET inhibitor, in inflammatory myofibroblastic tumours (IMT) with *ALK* translocations. While at the time of the meeting there were only retrospective clinical studies to support the activity of the drug in this condition,[23] the results of the completed EORTC phase II study with crizotinib in IMT are now available (NCT01524926).[24] Unfortunately, only general preclinical data are available to support the activity reported in retrospective (ie, sunitinib[25]) and prospective controlled (ie, cediranib[26]) studies on antiangiogenics in alveolar soft part sarcoma, a disease marked by high vascularity and resistance to conventional chemotherapy. Similarly, there are no preclinical data to support the retrospective evidence on the efficacy of sirolimus in epithelioid haemangioendothelioma,[27] or the retrospective (ie, sunitinib[28]) and also uncontrolled prospective (ie, pazopanib[29–31]) data on antiangiogenics in SFT. Robust preclinical data are essential for accumulating evidence in rare histologies and potentially supporting drug approval. There was an agreement at the meeting on the need to work collectively to foster research and improve understanding of the biology underlying drug activity. There was also an agreement to work on consensus-development initiatives to help shape recommendations where direct evidence is formally weak.

The case of histiocytic and dendritic cell neoplasms was also discussed during the symposium. These are a very rare and heterogeneous group of diseases with haematological or mesenchymal derivation, which differ in histology, clinical presentation and biology. Pathologists and clinicians agree that histiocytic sarcoma, the most common subtype, and Langerhans cell sarcoma are high-grade aggressive diseases, but the behaviour of the remaining subtypes remains uncertain. Treatment of localised disease is based on surgery, with little data available on the value of radiation therapy and medical therapy. Sarcoma-like and lymphoma-like regimes are effective in some patients with advanced disease and hints of activity have been reported with MEK and BRAF inhibitors.[32 33] In order to better understand biology, natural history and define the optimal treatment strategy, an effort within the sarcoma domain of EURACAN has been deployed.

Among special entities, attention was dedicated to desmoid-type fibromatosis during the symposium. This is a rare fibroblastic, proliferative, locally aggressive disease with no metastatic potential. Surgical resection was historically the mainstay of treatment, but in the last 10 years its use has substantially declined, as studies have documented high chances of stable disease with no treatment, spontaneous regressions and a tendency towards LR after apparently adequate resections.[34] The value of systemic treatments for progressive or symptomatic patients was emphasised at the meeting. Significant responses have been reported with vinorelbine or vinblastine (with or without methotrexate), anthracyclines and sorafenib.[35–37] The best upfront treatment and the ideal sequence of compounds are uncertain. S. Bonvalot said there is still a role for surgery, particularly for the management of complications or unacceptable cosmetic issues. Surgery may also be considered when the diagnosis is unclear and disease progression could be life-threatening. Conversely, surgery should not be used in general to manage mild pain, recurrent disease, disease during pregnancy or postpartum or disease occurring with familial adenomatous polyposis.

New avenues in STS: epigenetics and immunotherapy

M. Gounder described how gene silencing through DNA hypermethylation at promoter and/or enhancer regions, mutation or post-translational modification of histones and deregulation of chromatin remodelling complexes are epigenetic mechanisms of oncogenicity across many different sarcoma types. Such epigenetic deregulation can result in the upregulation of oncogenes or the silencing of genes with tumour suppressor or cellular differentiation programming functions. Recurrent mutational deregulation of the SWI-SNF chromatin-remodelling complex is crucial to the development of certain STS subtypes such as epithelioid sarcoma, malignant rhabdoid tumour, synovial sarcoma and a subset of chordomas. The oncogenic role of epigenetic deregulation is recognised in an increasing proportion of other STS. For example, a Cancer Genome Atlas study identified a subset of dedifferentiated liposarcoma with a hypermethylated genome that is associated with

worse survival compared with hypomethylated tumours of the same subtype.[38] Dr Gounder summarised the growing number of drugs that target epigenetic abnormalities either directly or through synthetic lethality and highlighted the use of such agents in clinical studies of STS. The combination of histone deacetylase inhibitors with other treatment modalities is being investigated as a way to reverse chemoresistance or radioresistance in STS. EZH2 inhibitors have been associated with dramatic responses in tumours with deficient expression of the SWI-SNF member protein INI1.[39 40] The successful development of such drugs will likely depend on an improved understanding of the dynamic biology of epigenetic deregulation and the untangling of complex biomarker signatures.

The potential role of immuno-oncology in the management of STS is under investigation. R. Maki provided the meeting with an update on the underlying biology of antitumour immunity and the mechanisms by which cancers might escape this effect. S. D'Angelo summarised clinical trial data on immune checkpoint inhibitors in STS. While use of anti-PD-1/PD-L1 in STS has produced disappointing efficacy overall, there appears to be heightened sensitivity in certain subtypes including undifferentiated pleomorphic sarcoma and dedifferentiated liposarcoma.[41] Combining anti-PD-1/PD-L1 agents with anti-CTLA-4 drugs or tyrosine kinase inhibitors may broaden and enhance the effect of immune checkpoint inhibitors. J.Y. Blay discussed translational studies that have identified genomic and microenvironment factors within sarcomas that correlate with sensitivity to immunotherapy and may form the basis for clinically useful biomarkers. Meanwhile, L. Helman summarised ongoing efforts to exploit the presence of cancer-related antigens in certain STS subtypes with autologous T cell therapies engineered to specifically and avidly target tumour cells. W. Tap suggested which drugs and targets should feature in the next generation of STS immuno-oncology trials.

Massive parallel sequencing and pathological diagnosis

Sarcomas are rare tumours featuring a relatively simple karyotype in a distinct proportion of cases. This should make it possible to identify molecular alterations that improve diagnostic accuracy and can be translated into clinically useful predictive biomarkers.

In this scenario, massive parallel sequencing (MPS) is a new tool with the potential to refine the pathological diagnosis of STS and identify novel therapeutic targets. The implications of recently published studies and the value of MPS in sarcoma were debated during the symposium. The results of two large retrospective studies were reported in 2017. A study in 5635 patients with sarcoma suggested that MPS significantly improves diagnosis and selection of therapies. MPS changed 8% of initial pathological diagnoses and actionable mutations were identified in 57% of patients. It should be noted, however, that approximately 900 patients lacked a precise diagnosis.[42] Similarly, an analysis of the mutational and copy number profiles of 587 patients with STS found that 93% had at least one actionable mutation, copy number alteration and/or fusion gene.[43] The data appear promising, but it is unclear what 'actionable' means for clinical practice, since specific drugs may be unavailable or (in many European countries) off-label use may be prohibited and in any case their actual value remains to be determined.[44 45]

Molecular diagnostic tests are currently applied to contribute to the diagnosis in selected groups of sarcomas such as translocation-related ones. Predicted biomarkers are still limited, best examples being represented by *KIT/PDRGFA* in GIST and *ALK* in IMT. A targeted MPS approach (meaning a selection of a limited number of molecular aberrations to be screened routinely) currently seems to be reasonable in GIST and in undifferentiated round cell sarcomas. In all other situations, a combination of immune-morphology and selective molecular analysis may still represent the most effective approach, but of course feasibility and costs could change this state of affairs in the near future.

The hyperbolic promises of 'precision medicine' has been boosted to suggest a 'disease-agnostic' approach, aimed to the mere identification of actionable molecular targets across histologies. There was a general agreement during the meeting that while it is worth screening for promising new specific targets such as *NTRK*, there is insufficient evidence that systematic MPS-based analysis in sarcoma is clinically useful. The routine role of MPS still remains undetermined.

In terms of 'discovery', two of the main diagnostic contributions of MPS have been the discoveries of STAT6 in SFT and MUC4 in low-grade fibromyxoid sarcoma. These are sensitive and acceptably specific immunomarkers that significantly improve the quality of sarcoma diagnosis.

In conclusion, immunomorphology and molecular genetics still represent the mainstay of sarcoma diagnosis. A rational use of MPS molecular approaches is certainly contributing to elucidating sarcoma pathobiology. Evidence that a disease-agnostic systematic screen of actionable mutations is clinically relevant is still lacking.

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