



Challenges in the Management of Metastatic Soft Tissue Sarcomas: where are we going?



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Abbreviations: STS: Soft Tissue Sarcoma; LMS: Leiomyosarcoma; LPS: Liposarcoma; UPS: Undifferentiated Pleomorphic Sarcoma; ASPS: Alveolar Soft Part Sarcoma; PEComa: Perivascular Epithelioid Tumor;DDLPS: Dedifferentiated Liposarcoma; NGS: Next Generation Sequencing; TMB: Tumor Mutational Burden; MFS: Myxofibrosarcoma; TRK: Tropomyosin Kinase; ES: Epithelioid Sarcoma

Introduction

Soft tissues sarcomas (STS) are a heterogeneous group of diseases with more than 70 entities described in the last WHO classification [1] and 13,040 estimated new cases in the US in 2018 [2]; the most common subtypes, excluding gastrointestinal stromal tumors, are represented by leiomyosarcoma (LMS), liposarcoma (LPS) and undifferentiated/unclassified sarcomas. Four new drugs have been approved by the FDA for the treatment of metastatic STS since 2012: olaratumab in the first line setting, in combination with doxorubicin; [3] pazopanib, a tyrosine kinase inhibitor for all subtypes but adipocytic tumors [4]; trabectedin for LMS and LPS [5]; eribulin for LPS [6] (the last three drugs were all approved for after prior chemotherapy).

During the last several years it has become progressively more clear that different subtypes of STS may respond differently to distinct treatments; one of the oldest examples in this regard comes from angiosarcoma that is known for its sensitivity to paclitaxel; additional examples include alveolar soft part sarcoma (ASPS) for its sensitivity to tyrosine kinase inhibitors and, most recently, to check point inhibitors; malignant perivascular epithelioid tumors (PEComa) that may respond to mTOR inhibition with drugs such as sirolimus or inflammatory myofibroblastic tumors to crizotinib and so on.

Immunotherapies based on check-point inhibitors are currently revolutionizing the way we treat multiple malignancies. The first demonstration of efficacy of immunotherapy in cancer actually comes from a patient with a neck sarcoma, back in

1891, who had a complete response after injection of a culture of streptococcus erysipelas [7]. Two recent prospective phase 2 studies explored the activity of checkpoint inhibitors in STS: the response rate was 18% (7/40) for pembrolizumab alone [8], 5% for nivolumab alone (2/38) and 16% (6/38) for nivolumab plus ipilimumab [9].

During the last few years, next generation sequencing (NGS) has shown the potential to impact the diagnosis and treatment of STS positively; a retrospective analysis of 5,635 patients worldwide included 56 different histologies; subjects have been profiled for 405 cancer-related genes in the DNA and 265 gene rearrangements in the RNA; 1165 fusions and more than 60,000 mutations were found; up to 42% of patients had some type of alterations that made them eligible for a targeted therapy in the context of a "basket" trial such as the NCI-MATCH trial [10].

Additional useful information from NGS analysis is represented by the tumor mutational burden (TMB); TMB has been associated with response to check-point inhibitors in multiple malignancies such as melanoma and non-small cell lung cancer. In an analysis of 100,000 human cancer genomes, sarcomas generally have showed relatively low TMB, but cases with high TMB have also been reported [11], this information may be of particular interest in less frequent histologies for which genomic data is very limited.

A comprehensive and integrated genomic characterization of adult STS has been recently published by the Cancer Genome

Atlas Research Network [12]: 206 sarcomas, representing 6 major types were analyzed through a multi-platform molecular approach. Copy number changes with low mutational loads and only a few genes highly recurrently mutated were noted across all subtypes (TP53, ATRX, RB1). Generally, deletions and mutations in tumor suppressor genes were more common than amplifications and mutations in oncogenes. Specific pathway activation with distinct molecular subtypes associated with clinical outcomes were found in dedifferentiated liposarcoma (DDLPS) and soft tissue LMS; furthermore, a study of the tumor immune microenvironment through DNA methylation and mRNA profiling revealed immune cell infiltration in genomically complex DDLPS, LMS, undifferentiated pleomorphic sarcoma (UPS) and myxofibrosarcoma (MFS). Of note, objective responses to check-point inhibitors in prospective clinical trials have been reported in the aforementioned subtypes with 4/10UPS and 2/10LPS responding to pembrolizumab, 2LMS, 1MFS, 2UPS out of 38 patients responding to nivolumab + ipilimumab, 1LMS out of 38 patients responding to nivolumab alone. Additional histologies that showed responses in these trials included one angiosarcoma treated with nivolumab + ipilimumab, one ASPS treated with nivolumab alone and one synovial sarcoma who received pembrolizumab [8,9].

Classically, cancer patients have been enrolled into clinical trials based on specific histologic and age criteria. Basket trials with a focus on peculiar genomic characteristics are now inducing a paradigm shift in the treatment of many cancers; rare cancers such as STS will especially benefit from this new trial design because of the obvious challenges in developing prospective studies in uncommon disease.

One of the most successful examples in this regard is the clinical development of larotrectinib, a potent and selective small-molecule inhibitor of tropomyosin kinase (TRK) proteins. In a cohort of 55 patients with 17 different types of cancers including 18 patients with STS, larotrectinib showed objective responses in 75% of patients with 7 complete responses. Of note, two pediatric patients with locally advanced fibrosarcoma were able to undergo limb-sparing surgery with curative intent after pre-operative treatment [13]. Other stories such as the development of MDM2 or CDK4 inhibitors for dedifferentiated LPS, have been less successful so far, but multiple target therapies are in clinical development. Additional treatment strategies include targeting the epigenetic cellular machinery; one example comes from the use of EZH2 inhibitors in INI1 negative tumors such as epithelioid sarcoma (ES). ES is notoriously a very aggressive and chemo-resistant STS subtype for which only surgical resection has shown to be potentially curative to date. An ongoing phase 2 multicenter trial is exploring the activity of the EZH2 inhibitor Tazemetostat in patients with INI1 negative tumors including ES; preliminary results presented at the 2017 ASCO meeting showed one partial response in ES [14]. Interestingly, one transient partial response to nivolumab and pazopanib has been

noted in a patient with ES in a recent retrospective series [15].

Conclusion

In conclusion, new genomic tools and trial designs are refining the diagnosis and treatment of STS increasing the knowledge on these heterogeneous diseases and providing new hope to patients.

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