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Future directions in soft tissue sarcoma treatment

Francis Hall*, Victor Villalobos, Breelyn Wilky

Department of Internal Medicine, Division of Medical Oncology, University of Colorado Denver Anschutz Medical Campus, Aurora, Colorado

A B S T R A C T

Sarcoma is a broad term for mesenchymal malignancies that arise from soft tissue or bone. Despite classification by histologic subtype, clinical behavior and response to therapy have great variability. Modern genetic sequencing techniques have been able to identify additional genetic variability and subsequently new targeted therapies. In this review, we discuss the current state of STS diagnostics and treatment and explore some of the more promising areas in which progress is being made. We discuss therapies targeting PDGFRα/KIT, β-Catenin/APC/NOTCH, IDH-1/2 mutations, MDM2 amplifications, EZH2/INI1 expression loss, ALK fusion, and ASPSCR1-TFE3 fusion. We also discuss the progress that has been made within immunotherapies. While soft tissue sarcomas still portend a poor prognosis, these targeted therapies and immunotherapies provide treatment with less toxic side effects.

A R T I C L E I N F O

Keywords: Sarcoma; Soft tissue sarcoma; Targeted therapy; Immunotherapy; PDGFRα; KIT; β-catenin/APC/NOTCH; IDH mutation; MDM2; EZH2/INI1; ALK fusion; ASPSCR1-TFE3 fusion

Introduction

Sarcoma is a broad term for mesenchymal malignancies arising from soft tissue or bone and includes more than 80 histologic subtypes, despite only accounting for less than 1% of adult malignant neoplasms.[1,2] Subtypes have been traditionally broken down into whether the tumor arises from bone vs soft tissue, and further by the mesenchymal cell of origin. While histo-

* Correspondence to: Francis Hall, MD, Department of Internal Medicine, Division of Medical Oncology, University of Colorado Denver Anschutz Medical Campus, Mail Stop, 13001 E 17th Pl B119, Aurora, CO 80045.
E-mail address: francis.hall@ucdenver.edu (F. Hall).

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logic subtype has been the traditional way of classifying sarcomas, the clinical behavior within various subtypes of sarcoma can be often vary widely (ie, well-differentiated liposarcoma vs myxoid/round cell liposarcoma).[3] Development of modern genetic sequencing techniques has also identified significant genetic heterogeneity even within the same histologic subtype, further complicating classification of sarcomas. Despite this heterogeneity, the therapeutic standard of care for most metastatic soft tissue sarcoma (STS) has remained anthracycline-based chemotherapy, which brings with it substantial toxicity and variable efficacy.[4-6] Even with the recent development of several novel chemotherapeutics, the prognosis of metastatic STS remains poor: 2-year median survival of 38% and median survival of 18 months.[7,8] Fortunately, multiple developments in genetic sequencing, targeted therapies, and immunotherapies are driving progress within STS.[9] These advances encourage customization of therapies to each patient's clinical status, histologic subtype, and genetic mutational profile.[10,11] In this review, we will discuss the current state of STS diagnostics and treatment and explore some of the more promising areas in which progress is being made.

Diagnostics

Morphologic evaluation based on examination of histologic sections remains the gold standard for sarcoma diagnosis. However, there is frequent discordance among pathologists, particularly between referring institutions and sarcoma referral centers with expert bone and soft tissue pathologists. In one study, discordant diagnoses were reported in 25% of cases, over half of which had clinical significance and led to a change in the treatment plan.[12] While this has improved from older studies, it still poses a significant barrier to optimal care.[13] Diagnosis is often supplemented by immunohistochemistry, cytogenetics, and genetic sequencing. Since the 1960s and 70s when Nowel et al and Rowley published their findings of specific and recurrent genetic alterations in CML (ie, Philadelphia Chromosome), assessment of the oncologic genome has been a priority among cancer researchers.[14,15] Research efforts within sarcoma have revealed many genetic alterations in many subtypes of sarcoma, and these are becoming increasingly incorporated into the diagnostic paradigm.[4] For example, Shern et al looked at whole-genome, exome, and transcriptome sequencing of rhabdomyosarcomas. They found that 93% of their 147 tumor-normal pairs had alterations in the receptor tyrosine kinase RAS/PIK3CA associated networks. Moreover, they found that whether a PAX fusion is present is a better predictor of clinical behavior and prognosis compared to the alveolar or embryonal histology-based subtyping commonly used.[16,17] As molecular characterization is ongoing and multiple complexities have yet to be elucidated, it is still very important to have biopsies of newly diagnosed suspected sarcomas be evaluated by a pathologist with sarcoma clinical expertise.

Targeted treatments

PDGFRα/KIT

While conventional chemotherapy remains the backbone for many STS, new developments have focused on targeted therapy and immunotherapy. There is an increasing role for molecular testing to support certain diagnoses within STS. Additionally, detailed analysis of the genetic make-up of a patient's tumor has implications for targeted therapy.[9] Gastrointestinal stromal tumors (GIST) are a good example of effective targeted therapy within sarcoma. GISTs are a class of sarcoma that arise from the interstitial cells of Cajal, gastrointestinal cells that serve as pacemakers for smooth muscle contraction. Historically, GISTs have been resistant to traditional chemotherapy and radiotherapy.[5] GIST tumors were found to contain mutations in KIT and PDGFRα (80% and 5%-7%, respectfully), which is critical to distinguish them from other sarcomas of the gastrointestinal organs such as leiomyosarcoma. Importantly, small molecule tyrosine kinase inhibitors have been found to be very effective for GIST based on these driving

mutations.[18-21] Imatinib (a tyrosine kinase inhibitor of KIT and PDGF-R) is the standard of care first line therapy for GISTs in the neoadjuvant, adjuvant, and metastatic setting.[20,21] In metastatic GIST, sunitinib and regorafenib can be used after progression on imatinib.[22,23]

Not unexpectedly, GISTs can develop resistance to these therapies.[24] Imatinib, sunitinib, and regorafenib are type II TKIs of KIT and PDGFRα, binding to the inactive conformation.[25] Mutations that cause the protein to be shifted in the active conformation are less responsive to imatinib, sunitinib, and regorafenib.[25] Avapritinib (BLU-285) is a TKI that has remarkable activity against imatinib-resistant GISTs driven by the PDGFRα D842V mutation, and is being studied in an ongoing phase 3 trial against regorafenib in the third-line setting.[25,26] DCC-2618 is also currently being studied in a phase 3 trial compared to sunitinib, after promising results in earlier studies.[9,27]

Outside of GIST, early data suggested that PDGFRα may be a target.[28] The phase II trial by Tap et al published in *Lancet* 2016 reported that olaratumab (a monoclonal antibody against PDGFRα) in combination with doxorubicin had a median PFS (the primary endpoint) of 6.6 vs the 4.1 months seen in the doxorubicin alone arm.[29] Furthermore, the median overall survival was 26.5 vs 14.7 months (HR 046; P= 0.0003). However, levels of PDGFRα did not correspond to response rates. This trial resulted in the approval for olaratumab and doxorubicin for all STS by the US Food and Drug administration (FDA) in late 2016. Unfortunately, data released prior to the publication of the phase III randomized trial comparing olaratumab and doxorubicin to doxorubicin did not confirm the clinical benefit of olaratumab in combination with doxorubicin as compared to doxorubicin.[30] Olaratumab has subsequently been removed as an FDA-approved option for STS in early 2019.

Beta-catenin/APC/NOTCH

Desmoid tumors are benign, locally invasive tumors of musculo-aponeurotic origin that arise within the abdominal or chest wall, intra-abdominally, or in the extremities.[31-33] They are bland tumors that are driven by aberrations in the WNT pathway by stabilizing mutations in beta-catenin or by mutations that inactivate APC.[34] Despite their lack of metastatic potential, desmoid tumors can behave aggressively, causing considerable morbidity with high rates of local recurrence despite wide excisions.[35] The decision to treat desmoid tumors is complex when taking into account the potential morbidity associated with surgical resection, the fact that 24% can undergo spontaneous regression with conservative management, and that some patients will not respond to local or systemic therapies.[36] Gounder et al published their findings from a phase III trial investigating sorafenib vs placebo.[37] They found a 2-year progression-free survival rate of 81% vs 36% in the placebo group. Notably, about 40% had previous systemic therapy and about 50% had previous surgery. Nirogacestat (PF-03084014) reversibly inhibits gamma secretase, a protein involved in cleaving different protein complex: NOTCH, E-cadherin, amyloid precursor protein, and others.[38] Early studies found response rates of 29%-71%, with longer term disease control rates near 96%.[35,38] This drug is currently being studied in a placebo-controlled phase III clinical trial for desmoid tumors (NCT03785964).

IDH-1/2 mutation

Isocitrate dehydrogenase 1 and 2 (IDH-1/IDH-2) is an enzyme in the cytosol, mitochondrion and peroxisome that uses isocitrate to produce alpha-ketoglutarate and CO_2.[39] Mutation in the R132 position of IDH1 causes the creation of an oncometabolite (2-HG). Accumulation of 2-HG effectively causes dedifferentiation of the cell.[40] This protein is mutated in 54%-100% of chondrosarcomas.[41,42] Tap et al published a phase I study of AG-120, an IDH-1 mutant enzyme inhibitor for solid tumors with IDH1 mutations that resulted in 55% disease stabilization rate, with 31.5% of patients stable for at least 6 months.[43] Notably, there were no responses seen, but given the paucity of treatment options for chondrosarcomas, this well-tolerated therapy

holds promise. Future studies are being planned for chondrosarcoma using other novel IDH1/2 inhibitors.

MDM2 amplification

Well-differentiated liposarcomas (WD LPS) and dedifferentiated liposarcomas (DD LPS) share similar genetic mutations, but phenotypically behave very differently.[3] DD LPS grows quicker, can invade and obstruct structures, and may be more responsive to chemotherapy. WD LPS is more indolent and typically not responsive to chemotherapy. Both DD LPS and WD LPS frequently have mouse double-minute 2 homolog (MDM2) amplifications (94% of the time).[44] MDM2 is responsible for ubiquitination of the tumor suppressor protein p53 for proteasomal degradation.[45] Nutlins are a class of drugs that inhibit MDM2-mediated suppression of p53.[46] In a phase I trial by de Jonge et al, the nutlin SAR405838 was evaluated in patients with DD LPS, leading to 71% (22 of 31) of patients achieving stable disease, but no objective responses.[47] Another nutlin, RG7112 (a nutlin) was studied in the neoadjuvant setting in 20 patients with WD LPS or DD LPS.[48] There was a partial response in 1 patient, and stable disease in 14 patients. All of the patients with progression of disease had DD LPS. While inhibition of MDM2 may increase levels of p53, it does not appear to make the p53 protein more active, and combination therapies may be required in the future.

EZH2/INI1 loss

INI1 is a tumor suppressor gene that inhibits the oncogene EZH2.[49] INI loss is associated with some STS subtypes (epithelioid sarcoma, rhabdoid tumors) in addition to other solid tumor malignancies (ovarian small cell carcinoma and renal medullary carcinoma).

Gounder et al investigated the use of tazemetostat (an EZH2 inhibitor) in a number of tumor subtypes, all with INI1 loss.[50,51] There were 5 cohorts included in the study, 1 of which was all epithelioid sarcoma patients ($n = 31$). Four of 31 patients achieved partial response, 2 of which were durable (>32 weeks).

ALK fusion

Inflammatory myofibroblastic tumors (IMT) frequently express ALK fusions, which can be targeted with crizotinib. Mosse et al treated 14 children with IMT with crizotinib. They saw an 86% ORR, and 36% achieved a complete response.[52] However, ALK fusion negative IMT patients have a much lower response rate (14%).[53]

ASPSCR1-TFE3 fusion

ASPSCR1-TFE3 fusions are characteristic of alveolar soft part sarcomas (ASPS).[54] Downstream transcriptional targets of this fusion protein include various angiogenic targets, and TKIs against vascular endothelial growth factor receptors (VEGF) have proven to be the most effective strategies for this highly chemotherapy-resistant subtype. Judson et al compared the pan-VEGF inhibitor cediranib vs placebo in ASPS in a randomized phase II trial.[55] The ORR was 21% in the cediranib group (at week 24) compared to 0 in the placebo group. Median PFS was 10.8 months vs 3.7 months. One-year survival was 96% for the cediranib group and 64.3% for the placebo group. Toxicity included 23% grade III hypertension and 14% grade III diarrhea, known class effects from VEGF inhibition. An ongoing phase III trial is evaluating the VEGF TKI anlotinib, in ASPS as well as leiomyosarcoma and synovial sarcoma (NCT03016819).

Immunotherapy

Immunotherapy, including immune checkpoint inhibitors, has become an exciting new treatment strategy for many solid tumors, and has shown remarkable activity in multiple chemotherapy-refractory cancers, even inducing durable remissions in some malignancies. Immune checkpoint inhibitors against PD-1/PD-L1 and CTLA-4 are just beginning to be explored in sarcomas, with meaningful and durable responses observed in some patients, but overall responses are less than 20%. Biomarkers of response to immune checkpoint inhibitors in sarcoma remain an area of great interest.[56-58]

PD-1/PD-L1

The SARC028 trial published by Tawbi et al in *Lancet* 2017 investigated the anti PD-1 antibody, pembrolizumab in selected STS and bone cancer sarcoma subtypes refractory to prior therapies.[57] Seven of the 40 patients with STS had an objective response including 4 of 10 patients with undifferentiated pleomorphic sarcoma (ORR 40%), 2 of 10 patients with dedifferentiated (ORR 20%), and 1 of 10 synovial sarcoma patients (ORR 10%). However, no patients with leiomyosarcoma (n = 10) had a response. Anemia appeared to be the most frequent grade 3 or more adverse event. Minimal activity was seen in the bone sarcoma arm which included patients with Ewing sarcoma, osteosarcoma, and chondrosarcoma.

D'Angelo et al evaluated nivolumab (anti-PD-1 antibody) with or without ipilimumab (anti-CTLA-4 antibody) in patients with locally advanced, unresectable, or metastatic sarcomas.[58] Patients were randomized to nivolumab alone or nivolumab with ipilimumab. Two of 38 patients randomized to the nivolumab alone group responded (5%), compared to 6 out of 38 patients randomized to the nivolumab with ipilimumab (16%). Twenty-nine of 42 patients (69%) on the nivolumab monotherapy group had disease progression at week 12 as compared to 18 of 42 patients (43%) in the combined therapy group. The types of sarcomas that had a response included uterine leiomyosarcoma (N = 1), nonuterine leiomyosarcoma (N = 1), myxofibrosarcoma (N = 1), undifferentiated pleomorphic sarcoma (n = 2), malignant fibrous histiocytoma (n = 2) and angiosarcoma (n = 1). Median OS in the monotherapy group was 10.7 months, compared to 14.3 months in the combined therapy group. Notably, more grade 3-4 treatment-related adverse events occurred in the combination therapy group (14% vs 7%).

Toulmonde et al hypothesized that the synergistic immunomodulatory effect of metronomic cyclophosphamide (CP) and an anti-PD-1 antibody could be beneficial in patients with advanced STS and GIST.[59,60] This single-arm phase II trial looked at 4 cohorts: unresectable leiomyosarcoma (cohort 1), undifferentiated pleomorphic sarcoma (cohort 2), other sarcomas (cohort 3), and GISTs (cohort 4). Patients were given 50 mg cyclophosphamide orally twice daily for 7 days on then 7 days off; with 200 mg pembrolizumab given intravenously on day 8 of a Q21 day cycle. Only 1 of 50 patients assessable for efficacy met criteria for partial response, and 3 were progression-free at 6 months. Nearly all sarcomas enrolled demonstrated strong infiltration by immunosuppressive M2 macrophages and IDO1 expression, illustrating the complexity of the immune microenvironment in sarcomas and the need for further study of potential resistance mechanisms.

Despite these disappointing outcomes for all-comers, there remain important signals of activity in several sarcoma subtypes that warrant further investigation. In a phase II study of combination VEGF inhibitor axitinib plus pembrolizumab, remarkable activity was seen in patients with ASPS, with an objective response rate of 54.5%.[61] Additionally, cutaneous angiosarcomas have demonstrated remarkable activity with immune checkpoint inhibitors in small case reports and series, leading to plans for clinical trials to further confirm this potential benefit. In other solid tumors, immunotherapy combinations with chemotherapy, radiation, and other targeted agents have shown improved responses over checkpoint inhibitors alone, and multiple clinical trials for sarcomas are also exploring these potential strategies to boost the efficacy of immunotherapy.

Summary

Sarcomas have long been in dire need of novel therapies, given the aggressive nature and poor prognosis in the metastatic setting. One of the major limitations to drug development is that clinical trials tend to enroll a large number of sarcoma subtypes. It is critical to remember that in reality, we are dealing with over 100 different cancers, despite the common mesenchymal origin. With the advent of innovation in genetic profiling and cytogenetics, we are beginning to appreciate the remarkable complexity and heterogeneity in these diseases, and beginning to derive more rationale therapies based on biology rather than histologic appearance. Rather than committing patients to a one-size-fits-all treatment approach, early referrals to sarcoma centers are critical to ensure these patients are accurately diagnosed, and have the opportunity to be evaluated for clinical trials, including targeted therapies, immunotherapies, and novel cytotoxic agents.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.currproblcancer.2019.06.004.

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