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Soft tissue sarcomas in the precision medicine era: new advances in clinical practice and future perspectives

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Abstract

Soft tissue sarcomas (STSs) represent a rare and heterogeneous group of solid tumours derived from mesenchymal progenitors and account for 1% of all adult malignancies. Although in the last decade anthracycline-based chemotherapy single agent or in combinations has been able to improve clinical benefits, prognosis is still poor and STSs represent an important unmet medical need. Continuous advances in cancer genetics and genomics have contributed to change management paradigms of STSs as it occurred for other solid tumours. Several treatments have been recently developed with the specific aim of targeting different cell pathways and immune-checkpoints that have been recognized to drive tumour progression. The following attempts to provide a review of literature focusing on the available data concerning novel treatments and future prospective for the management of metastatic STSs.

Keywords Soft tissue sarcomas · Immune-checkpoint inhibitors · Pembrolizumab · Eribulin · Olaratumab · Targeted therapy

Introduction

Soft tissue sarcomas (STSs) represent a rare and heterogeneous group of solid tumours derived from mesenchymal progenitors and account for 1% of all adult malignancies [1]. Approximately 80% of sarcomas arise from soft tissue and viscera, whereas the remaining 20% originate from bone. STSs potentially may occur at all body anatomic sites, even though the majority arise from the extremities. An observational study of the American College of Surgeons showed that among a cohort of 4550 patients suffering from sarcomas, 46% originate from thigh, buttock and groin, 13% by

upper extremities, 18% torso, 13% retroperitoneum and 9% head and neck [2].

As classified by the World Health Organization (WHO), the group of STSs comprise more than 100 different histologies according to the presumptive tissue in origin [3]. Histological diagnosis is crucial to define staging, prognosis and to deliver appropriate therapy. Unfortunately, sometimes it causes a diagnostic challenge for pathologist, particularly when the diagnostic material is a small biopsy and when clinical information is incomplete. Although in the past STSs were considered a whole entity and treated similarly, consensus is emerging that the choice of treatment for advanced disease should be histology driven. After the development of distant metastasis the median overall survival (OS) is 12–19 months, and almost 20% of patients are still alive at 3 years [4]. Systemic therapy provides palliation and prolongs survival for patients with metastatic or unresectable STSs. For patients with a good performance status and STS histology that is known to have sensitivity to anthracyclines (liposarcoma, leiomyosarcoma, synovial sarcoma, pleomorphic or undifferentiated sarcoma, malignant nerve sheath tumour, angiosarcoma), anthracycline-based chemotherapy represents the standard of care for first-line setting [5]. For patients ineligible to anthracycline

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combination due to a poor performance status or extensive comorbidity, pegylated liposomal doxorubicin, gemcitabine alone or in combination and dacarbazine are reasonable options [6–8]. A histology-driven approach should be regarded for patients who progressed after first-line therapy. Weekly paclitaxel seems to be useful for advanced angiosarcomas [9]; synovial sarcomas are sensitive to alkylating agents as ifosfamide [10]; sunitinib appears to be active in patients with solitary fibrous tumour and alveolar sarcoma, clear cell sarcoma and extra-skeletal myxoid chondrosarcoma [11–13]; gemcitabine plus docetaxel regimen is active on uterine leiomyosarcomas [14]. Trabectedin is approved for the treatment of leiomyosarcomas and liposarcomas previously treated with anthracycline-based chemotherapy [15]. Pazopanib might be considered for STSs other than liposarcomas for patients progressing on first-line chemotherapy (including anthracyclines) [16].

Although these treatments or chemotherapy combinations have been able to improve clinical benefits, prognosis is still poor and STSs represent an important unmet medical need.

Continuous advances in cancer genetics and genomics have contributed to change management paradigms of STSs as it occurred for other solid tumours. Several treatments have been recently developed with the specific aim of targeting different cell pathways and immune-checkpoints that have been recognized to drive tumour progression (Table 1). The following attempts to provide a review of literature focusing on the available data concerning novel treatments and future prospective for the management of metastatic STSs.

Methods

A literature search using PubMed was carried out with no date restriction up to November 2017. The search strategy has included the keywords "soft tissue sarcomas", "Olaratumab", "Eribulin", "immune-checkpoint", "targeted therapy". A computerized search of the abstracts reported at ASCO and ESMO library, and the clinical trial database on the website http://www.clinicaltrial.gov was performed to identify relevant unpublished studies and ongoing trials. Finally, a crosscheck references from review articles and relevant studies on the same topic were performed to confirm retrieval of all pertinent trials.

Eligible studies had to fulfil the following criteria: randomized prospective phase II–III trial assessing new or recently approved treatments for patients with metastatic STSs.

Table 1 Main characteristics of clinical trials carried out on metastatic STS patients

Clinical trial	Drug	Histological type	Study design	Primary endpoint	N. patients	Results
Tap et al. [21]	Olaratumab + doxorubicin vs doxorubicin	LMS, UPS, LS, AS, SS, NFS, F, other	PHASE Ib/II	PFS	133	mPFS: 6.6 vs 4.1 months ($p=0.0615$) mOS: 26.5 vs 14.7 months ($p=0.0003$) ORR: 18.2 vs 11.9% ($p=0.3421$)
Wagner et al. [26]	Olaratumab	GISTs previously treated with a TKI	PHASE II	12-week tumour response	30	12-week tumour response: 50% of SD at 12-week in PDGFRα mutant patients vs 14.3% in PDGFRα negative
Schöffski et al. [31]	Eribulin	LMS, SS, LS, other	PHASE II	12-weeks PFS	128	12-week PFS: 46.9% LMS vs 31.6% LS
Schöffski et al. [32]	Eribulin vs dacarbazine	LS, LMS	PHASE III	OS	452	mOS: 13.5 vs 11.5 months ($p=0.0169$) mPFS: 2.6 vs 2.6 months ($p=0.23$)
Tawbi et al. [38]	Pembrolizumab	LS, LMS, ES, SS, PS, CS, OST	PHASE II	PFS	84	ORR: PS: 40 vs LS: 20%, SS: 10%

LMS leiomyosarcoma, *UPS* undifferentiated pleomorphic sarcoma, *LS* liposarcoma, *AS* angiosarcoma, *SS* synovial sarcoma, *NFS* neurofibrosarcoma, *F* fibrosarcoma, *ES* Ewing's sarcoma, *PS* pleomorphic sarcoma, *CS* chondrosarcoma, *OST* osteosarcoma, *TKI* tyrosine kinase inhibitor, *(m)OS* (median)overall survival, *(m)PFS* (median) progression-free survival, *ORR* objective response rate

Retrospective studies and case reports were excluded from the analysis. No language restriction was applied.

Olaratumab

Platelet-derived growth factor (PDGF) and PDGF receptor (PDGFR) are key regulators of oncogenesis process in many solid tumours, including mesenchymal stem cell differentiation, angiogenesis and tumour growth [17]. Several studies in vitro and in animal models showed that PDGFRα inhibition leads to an arrest of tumour proliferation and spread [18]. Olaratumab is a human monoclonal antibody (IgG1) that binding PDGFRα results in an inhibition of receptor autophosphorylation and downstream signalling [19]. Olaratumab alone or in combination with doxorubicin showed antitumor activities in human sarcoma xenograft models [20].

Basing on these data and rationale, an open-label phase Ib/II trial randomized 133 patients with histologically confirmed STSs diagnosis to receive olaratumab 15 mg/kg on day 1 and 8 plus doxorubicin 75 mg/m^2 day 1 three-weekly or doxorubicin alone [21]. Detection of a 50% improvement in progression-free survival (PFS) in the combination arm was the primary endpoint of the study. The proportion of leiomyosarcomas patients was well balanced between the two arms (36.4% versus 40.3% in experimental arm and doxorubicin arm, respectively). The median PFS was 6.6 months for patients treated with Olaratumab plus doxorubicin and 4.1 months for those under treatment with doxorubicin alone (HR 0.67, CI 95% 0.44–1.02, p 0.0615). This improvement met the protocol-defined significance level of 0.19. The independent review assessment showed similarly an advantage in favour of combination arm compared to control arm (8.2 versus 4.4 months, respectively, HR 0.67, CI 95% 0.40–1.12, $p = 0.0003$). The objective response rate was slightly higher for olaratumab plus doxorubicin than doxorubicin alone (18.2 versus 11.9%, $p = 0.3421$). Final analysis showed a significantly better OS for patients treated with the combination than doxorubicin alone (26.5 versus 14.7 months, respectively, HR 0.46, CI 95% 0.30–0.71). This achievement was consistent across the subgroup analysis including PDGFRα status, histological subtypes (leiomyosarcoma versus non-leiomyosarcoma) and number of previous treatments (0 versus ≥ 1). Infusion-related reaction (3%) was the main cause leading to Olaratumab discontinuation, whereas 5% of ejection-fraction decrease was the most common reason of discontinuation in doxorubicin group. Grade 3–4 occurred more frequently in the doxorubicin and olaratumab arm than in doxorubicin alone arm (42–31%). The most common adverse events in the combination arm include neutropenia, nausea, fatigue, vomiting and mucositis [21].

Despite clinical trial limitation due to the small sample size and heterogeneity of STSs histology, this finding is particularly notable given the little progress in improvement of median OS achieved for patients suffering from metastatic STSs. In a phase III trial, the combination doxorubicin plus high dose of ifosfamide improved PFS and response rate compared with doxorubicin alone in first-line therapy. However, this small benefit was achieved at expense of higher toxicities without any improvement in median OS (HR 0.83, $p = 0.76$) [22]. Therefore, the promising results of the randomized phase II trial lead FDA in October 2016 and EMA in November 2016 to the rapid approval of the combination olaratumab plus doxorubicin. Many ongoing clinical trials are assessing the activity of Olaratumab alone or in combination with chemotherapy regimen.

A randomized double-blind phase III ANNOUNCE trial is still recruiting 460 patients with advanced or metastatic STSs to receive olaratumab 15 mg/kg on day 1 and 8 plus doxorubicin 75 mg/m^2 on day 1 every 3 weeks versus doxorubicin 75 mg/m^2 plus placebo (NCT02451943). OS in whole population and in patients with leiomyosarcoma are the two primary objectives of the study.

A phase Ib trial (NCT02783599) is recruiting potentially 40 patients to receive Olaratumab 20 mg/m^2 alone for day 1 and 8 of the first cycle, then olaratumab 20 mg/m^2 in combination with doxorubicin 75 mg/m^2 for the second cycle and then olaratumab 15 mg/m^2 on the same schedule alongside doxorubicin for the third cycle. The primary endpoint was to molecularly characterize the circulating tumour cell pre- and post-olaratumab, and to analyze PDGFRα, PDGFRβ, and PDGF ligand changes.

A phase Ib/II (NCT02659020) trial is enrolling patients with metastatic STSs to assess safety, activity and efficacy of olaratumab in combination with gemcitabine and docetaxel. Dose finding to carry out a phase II trial was the primary endpoint. The phase II trial will randomly assign patients with metastatic STSs to receive olaratumab in combination of gemcitabine plus docetaxel or gemcitabine plus docetaxel and placebo. OS is the primary endpoint.

An open-label phase I trial (NCT03126591) is recruiting patients with metastatic STSs who has progressed to standard treatment to receive olaratumab plus pembrolizumab. Dose-limiting toxicity is the primary endpoint.

Most gastrointestinal tumours (GISTs) are driven by activating mutation in KIT tyrosine kinase receptor [23]. Although 80–90% of GISTs harbour KIT expression, some are not. This finding may be partially explained by the occurrence of activating mutation in the gene encoding the PDGFRα [24].

Most GISTs harbouring PDGFRα are primarily resistant to standard therapy due to D842V mutation that leads tumours not to be inhibited by approved treatments [25]. Given the benefits achieved by olaratumab targeting PDGFRα in preclinical models [20], a phase II trial evaluated tumour response to olaratumab in 30 previously treated
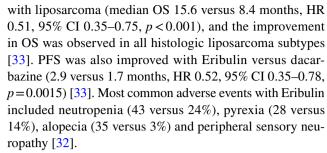
metastatic GISTs into two cohorts with or without PDGFRα mutations, respectively [26]. Twelve-week tumour response, PFS, OS and safety were outcome measures.

Although no objective disease responses were observed in the two cohorts, metastatic PDGFRα GISTs significantly experienced longer median PFS (32.1 and 6.1 weeks) and OS (NR and 24.9 weeks) than PDGFRα negative. Fatigue, abdominal pain, constipation, nausea, and headache were the most common related adverse events. Despite the limitation of this trial due to small sample size and inter-study heterogeneity to draw a definitive conclusion, these data provide the rationale for further study of PDGFRα-mutant GIST in larger study [26].

Eribulin

Eribulin, originally isolated from the marine sponge Halichondria Okadai, is a structurally modified analogue of halichondrin B. Eribulin's antitumor activity is due to microtubule dynamics inhibition. Irreversible binding of specific sites on the growing plus ends of microtubules results in the arrest of cancer cell growth and apoptosis via prometaphase blockage [27]. Moreover, Eribulin seems also to inhibit Wnt/β-catenin signalling, alter tumour vascularization resulting in higher perfusion and drug delivery, and reverse the epithelial to mesenchymal transition [28, 29]. Eribulin has been approved as standard of care for women with advanced or metastatic breast cancer who progressed after previous chemotherapy regimen [30]. Given Eribulin's antitumor activity in preclinical xenograft models of leiomyosarcomas and fibrosarcomas, a non-randomized phase II (study 17) trial assessed the activity and safety of Eribulin 1.4 mg/m^2 administered intravenously on days 1 and 8 every 3 weeks in four independent strata of 128 patients with mesenchymal tumours (leiomyosarcoma, liposarcoma, synovial sarcoma and other defined STS) [31]. PFS at 12 weeks was the primary endpoint. Activity was demonstrated in patients with liposarcoma (46.9% PFS at 12 weeks, 95% CI 29.1–65.3%) and leiomyosarcoma (31.6% PFS at 12 weeks, 95% CI 17.6–48.7%) [31].

An open-label phase III trial (study 309) randomly assigned 458 patients with metastatic intermediate or high-grade liposarcoma and leiomyosarcoma previously progressed on anthracycline-based chemotherapy to receive Eribulin 1.4 mg/m^2 day 1 and 8 or dacarbazine 850–1200 mg/m^2 every 21 days until disease progression or unacceptable toxicities [32]. OS was the primary endpoint. Eribulin significantly prolonged OS in whole population compared to dacarbazine (13.5 versus 11.5 months, HR 0.77, 95% CI 0.62–0.95), although PFS was similar in both arms (2.6 versus 2.6 moths HR 0.88, 95% CI 0.71–1.09, $p = 0.23$) [32]. In a pre-planned specific-histology subgroup analysis, benefits for eribulin were limited to patients

with liposarcoma (median OS 15.6 versus 8.4 months, HR 0.51, 95% CI 0.35–0.75, $p < 0.001$), and the improvement in OS was observed in all histologic liposarcoma subtypes [33]. PFS was also improved with Eribulin versus dacarbazine (2.9 versus 1.7 months, HR 0.52, 95% CI 0.35–0.78, $p = 0.0015$) [33]. Most common adverse events with Eribulin included neutropenia (43 versus 24%), pyrexia (28 versus 14%), alopecia (35 versus 3%) and peripheral sensory neuropathy [32].

Basing on these results, Eribulin has been approved in the USA and Europe for treatment of metastatic liposarcoma for patients who received prior anthracycline-based chemotherapy.

An ongoing single-arm (NCT03331250) phase II trial aims to assess the activity and effectiveness of Eribulin 1.4 mg/m^2 on day 1 and 8 administered intravenously three-weekly in patients with unresectable or metastatic angiosarcoma and hemangioendothelioma treated with at least one prior systemic treatment. Objective response rate is the primary endpoint, whereas PFS, disease control rate and treatment-related adverse events are the secondary endpoints. Primary completion date is estimated for May 31, 2021.

Immune-checkpoint inhibitors

Although the approval in the last decade of several drugs for the treatment of metastatic STSs [15, 16], these therapies did not achieve a substantial cure rate, leading to the development of new agents.

Response to conventional radiotherapy or chemotherapy is dependent on histology because some subtypes are chemo-resistant.

Cancer immunotherapy is gradually taking on a key role in the management of metastatic solid tumours, preventing the development of resistant clones to traditional chemotherapy and fostering tumour recognition by the immune system [34]. Historically, studies using cytokines or immune adjuvants provided small benefits for patients with metastatic STSs [35, 36].

In a randomized phase III trial, immunotherapy with adjuvant mifamurtide, a nonspecific immune stimulator, improves OS in patients with osteosarcoma [37]. Recently, the appeal for the improved clinical benefits in several solid tumours due to immune-checkpoint inhibitors leads to assess the safety and activity of these agents in STSs.

A two-cohort, single-arm, open-label phase II trial (SARC028) enrolled 84 patients with metastatic or unresectable STSs (leiomyosarcoma, poorly differentiated or dedifferentiated liposarcoma, Ewing's sarcoma, synovial sarcoma, undifferentiated pleomorphic osteosarcoma, dedifferentiated or mesenchymal chondrosarcoma) previously progressed up to three lines of chemotherapy to receive pembrolizumab 200 mg intravenously every 3 weeks until

progression or unacceptable toxicities [38]. Objective response was the primary endpoint. Almost 18% of patients with STSs had a clinically meaningful objective response, including 40% with undifferentiated pleomorphic sarcoma, 20% with liposarcoma, 10% with synovial sarcoma, and 5% with osteosarcoma. No patients with leiomyosarcoma had an objective response.

This result is consistent with data from a phase II trial on nivolumab in leiomyosarcomas that was stopped early because of futility, suggesting a detrimental effect of anti-PD1 single agent in this subset of patients [39]. Although the mechanism of immune resistance related to leiomyosarcoma histology is still unclear, PTEN loss and PI3K pathway may play a key role in this process [40]. A partial response was observed only in one patient with Ewing's sarcoma, suggesting that a small subset of patients suffering from this rare tumour may benefit from single-agent pembrolizumab.

The 12-week PFS was 55% (95% CI 40–70), which was significantly higher than the threshold of 40% expected for an active treatment for patients with STSs ($p = 0.039$). Most common adverse events were anaemia, decreased lymphocyte count and platelet count in the bone sarcoma group, whereas anaemia decreased lymphocyte count and prolonged activated partial thromboplastin time in the STSs group.

In an open-label multicentre phase II trial, 85 patients with metastatic STSs or osteosarcoma previously treated with standard chemotherapies were randomized to receive the anti-PD1 monoclonal antibody nivolumab with or without the anti-CTLA4 ipilimumab [41]. In a preliminary analysis reported at ASCO 2017 annual meeting, the combination nivolumab plus ipilimumab provided encouraging antitumor activities due to six confirmed responses in 38 treated patients and a median PFS of 4.5 months [41].

Given that none of these immune-checkpoint inhibitors is approved for advanced sarcomas, appropriately selected patients should be referred for clinical trials exploring these strategies. Many ongoing trials are still recruiting patients with metastatic STSs to assess the activity and efficacy of immune-checkpoint inhibitors in metastatic settings in combination with chemotherapy or neoadjuvant setting with radiotherapy (NCT03092323, NCT03092323, NCT03307616). Briefly, several ongoing phase I/II clinical trials are exploring the activity of pembrolizumab in combination with doxorubicin (NCT02888665, NCT03056001), axitinib (NCT02636725), olaratumab (NCT03126591). Dose finding, safety and objective response represent the main endpoint of these trials. Similarly, several ongoing phase I/II trials are assessing safety and tolerability of nivolumab single agent (NCT03316274) or in combination with Pazopanib (NCT03149120), ipilimumab (NCT03219671, NCT02982486, NCT02500797, NCT02304458, NCT02428192).

Conclusion

Histology-driven approach still remains the mainstay for the treatment of advanced unresectable or metastatic STSs. Although the utmost efforts in the development and quick approval of novel active and practice changing drugs [15, 16, 21, 32], prognosis is still poor [4]. Patients with advanced unresectable or metastatic STSs are ideal candidates for clinical trials to identify new prognostic and predictive factors of response to better select patients to maximize the effectiveness of more active single agents, combinations, or novel approaches.

Compliance with ethical standards

Conflict of interest All authors declare no conflicts of interest.

Ethical approval This article does not contain any studies with animals or humans performed by any of the authors.

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