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Update on systemic therapy for advanced soft-tissue sarcoma

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ABSTRACT

Background Soft-tissue sarcoma (STS) represents a rare group of mesenchymal neoplasms comprising more than 50 heterogeneous subtypes. Great efforts have been made to increase the understanding of the treatment of advanced STS (unresectable or metastatic disease). We set out to determine whether outcomes for patients with advanced STS have improved over time and to assess the current evidence for systemic therapy.

Methods In a scoping review, we evaluated the contemporary evidence for systemic treatment of advanced STS in adults (>18 years of age). Phase I, II, and III studies of systemic therapy for advanced STS published in the English language were included. After abstract and full-text review of seventy-seven studies, sixty-two trials met the inclusion criteria.

Results The number of clinical trials conducted and published in advanced STS has increased over the last 30 years. Although median overall survival has increased, attempts at improving first-line therapy through dose intensification, doublet chemotherapy, or alternative backbones have not been successful. The optimal therapy beyond anthracyclines remains a challenge, especially given the heterogeneity that grouping multiple STS subtypes within clinical trials creates. However, increasing numbers of agents are being studied, and several studies had shown isolated benefit in progression-free or overall survival.

Summary First-line systemic therapy with an anthracycline remains the standard of care for advanced STS. However, choice of subsequent therapy beyond anthracyclines remains challenging. Novel systemic therapies, use of molecular diagnostics to direct therapy, subtype-specific trials, and learnings from real-world retrospective data are all important for improving outcomes in patients with advanced STS.

Key Words Soft-tissue sarcoma, advanced; systemic therapy; anthracyclines

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INTRODUCTION

Soft-tissue sarcoma (STS) refers to a group of uncommon mesenchymal malignancies with more than 50 different subtypes[1]. In Canada, STS represents approximately 1175 new cases per year (0.6% of all cancer diagnoses) in adults[2]. The natural history and response to treatment between and within subtypes is heterogeneous. A large proportion of patients (14.5%–26.5%) present with *de novo* metastatic disease[3], and 40%–50% of patients with localized disease will develop metastasis[1]. Thus, patients with advanced STS, defined as those with unresectable or metastatic disease, represent a significant proportion of patients affected by STS.

Most published randomized trials in advanced STS include all subtypes of STS—the 5 most common histologic subtypes being liposarcoma (LPS), leiomyosarcoma (LMS), undifferentiated pleomorphic sarcoma (UPS), fibrosarcoma, and synovial sarcoma[4]. The rarity of sarcoma—and the even further rarity of individual subtypes of STS—has limited the ability to conduct large, histology-specific clinical trials to inform practice. Thus, most of the literature concerning the treatment of specific subtypes has focused on retrospective case series.

Outcomes for patients were very poor before the discovery, in 1973, that doxorubicin is active against STS[5], and anthracyclines have remained the backbone of standard-care treatment for advanced STS[6]. Since the 1970s, various trials have been conducted in hopes of improving patient outcomes or reducing adverse events through regimen intensification, non-anthracycline regimens, or use of alternative anthracyclines. In the present review, we aimed,

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through literature appraisal, to determine whether survival for patients with STS has continued to improve since the 1970s and to identify the optimum contemporary systemic treatment pathway for patients with advanced STS.

METHODS

Search Strategy and Selection of Studies

A scoping review was conducted using a literature search in PubMed with the keywords "soft tissue sarcoma," "metastatic," "unresectable," "systemic therapy," "immunotherapy," and "targeted agents" for 1987 to 15 May 2019. Specific searches based on drugs used in the treatment of STS were also performed. In addition, a search of ongoing clinical trials with the keywords "soft tissue sarcoma," "metastatic/advanced," and "systemic therapy" was performed at https://ClinicalTrials.gov/. We included studies published in the English language that involved adults (>18 years of age) diagnosed with advanced STS who were enrolled in prospective phase I, II, or III clinical trials and whose primary treatment was systemic therapy. Retrospective studies were excluded from the scoping review. Given well-established and distinctly different treatments, studies were excluded if the predominant histologic subtype was gastrointestinal stromal tumour, Ewing sarcoma, bone sarcoma (osteosarcoma, giant cell tumour of bone, chondrosarcoma), rhabdomyosarcoma, desmoid fibromatosis, and Kaposi sarcoma.

Data Extraction and Analysis

Titles were reviewed for relevance, and duplicates were removed. Abstract and full-text reviews of 152 studies were undertaken by AS, YW, and CS. Disagreements were resolved by consensus. Title, year published, trial type, number of patients, agents used, median progression-free survival (mPFS), median overall survival (mOS), clinical benefit rate (complete response, plus partial response, plus stable disease) and response rate [RR (complete response plus partial response)] were extracted from sixty-two studies. Number of studies per year, trial type, line of therapy, and type of systemic therapy were coded. Of thirty-two active clinical trials found at https://ClinicalTrials.gov/, AS reviewed all of them, and four were included in the final review. Descriptive statistics were used to generate figures (Figure 1) in the Excel software application (version 16.16.9: Microsoft Corporation, Redmond WA, U.S.A.).

Treatment Choices

Included studies were grouped by line of therapy (first line vs. beyond first line) to generate a summary of the evidence. When a systemic therapy was compared with doxorubicin, the study was coded based on the non-doxorubicin arm.

RESULTS

Studies Found

One hundred fifty-two trials from 1987–2019 underwent abstract and full text review, with sixty-two trials being included in the scoping review. Most were phase II trials ($n = 35$), with fewer being phase III trials ($n = 15$) or phase I trials ($n = 4$); the remaining trials were of mixed or undefined phase ($n = 6$), a meta-analysis ($n = 1$), or an undefined design ($n = 1$) [Figure 2(A)]. The number of published studies in this field has increased over time [Figure 2(B)], to 4–8 per year during 2012–2017 from 0–3 per year during 1987–2002. The types of systemic therapies studied for advanced STS have been increasing. The most commonly studied therapies included alkylating agents (ifosfamide, temozolomide, trabectedin), tyrosine kinase inhibitors, microtubule inhibitors (taxanes, eribulin), or anthracycline derivatives (epirubicin, liposomal doxorubicin, amrubicin) [Figure 2(C)]. Two studies—both published after 2017—focused on immunotherapy.

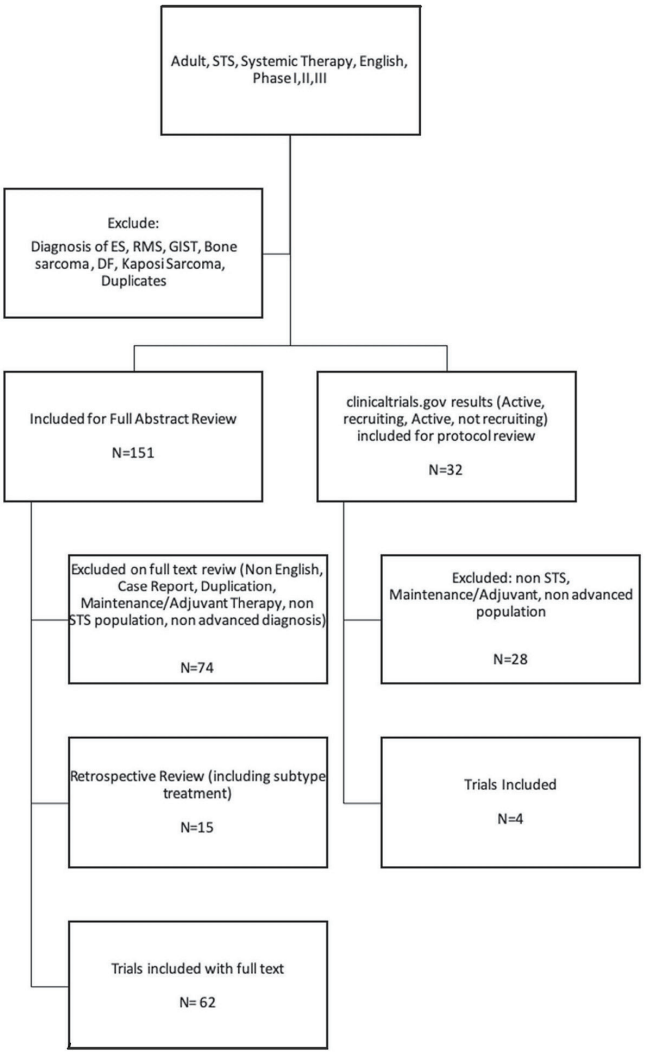

FIGURE 1 Consort diagram for the scoping review. STS = soft-tissue sarcoma; ES = Ewing sarcoma; RMS = rhabdomyosarcoma; GIST = gastrointestinal stromal tumor; DF = desmoid fibromatosis.

Outcomes

First Line

Compared with the mOS of 7.7–12.0 months with first-line doxorubicin reported by the Cochrane review in 2003[6], the mOS has steadily improved, with the most recently reported

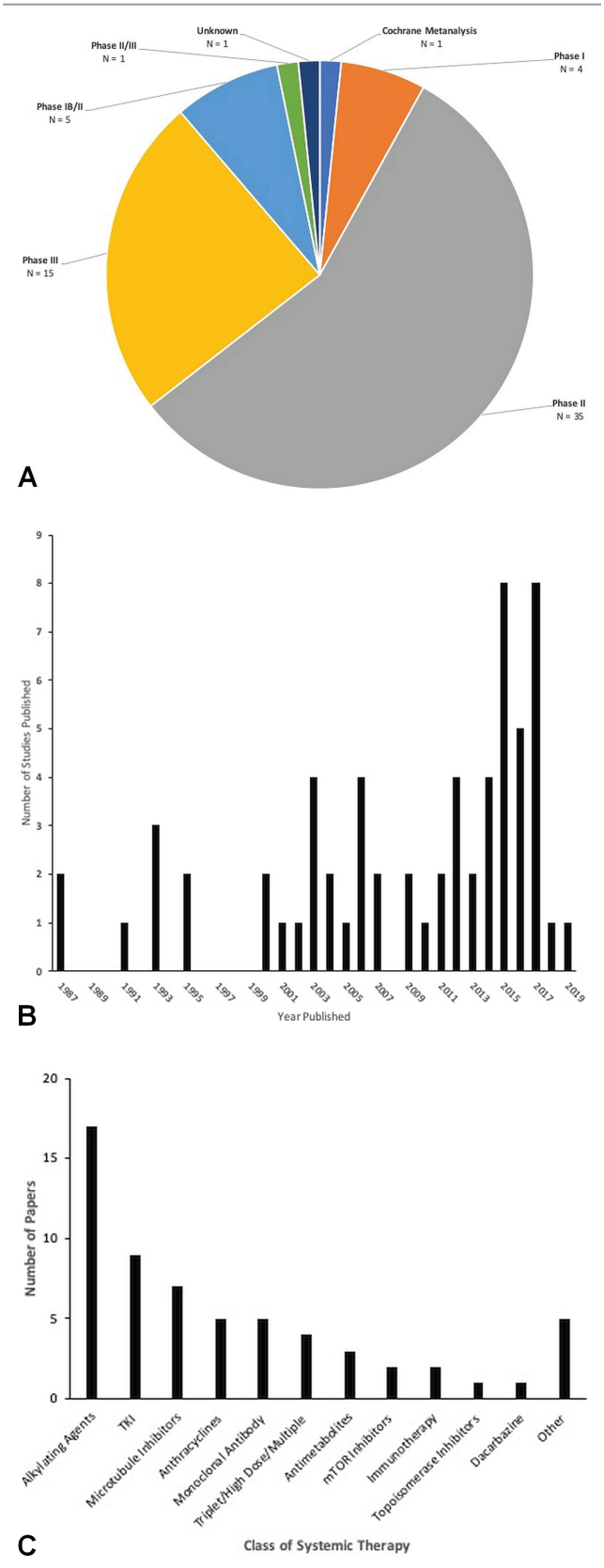

FIGURE 2 (A) Types of published study included (n = 62). (B) Trends in publication per year since 1987. (C) Class of systemic therapy used in the study. TKI = tyrosine kinase inhibitor.

mOS being 20.4 months for doxorubicin in a doxorubicin–olaratumab phase III trial[7,8] (Table I). By contrast, the mPFS has, overall, remained stable over time. Compared with doxorubicin, newer anthracyclines developed with the hopes of reducing toxicity have not demonstrated an improved mOS[18–22]. Furthermore, the RRs for comparisons with doxorubicin were all lower in older single-arm studies of gemcitabine (RR: 4%)[23], paclitaxel (RR: 12%)[24], perifosine (RR: 5%)[25], and temsirolimus (RR: 5%)[26]. The RR for single-agent ifosfamide at a dose of 12 g/m^2 was 17%; however, that regimen was associated with significant grades 3 and 4 toxicities[27].

Table I summarizes modern first-line trials comparing doxorubicin with doublet or novel systemic therapy backbones. Compared with doxorubicin alone, dose escalation or doublet chemotherapy regimens that, in large phase III trials, attempted to intensify treatment have not improved the mOS[6,11,13]. Compared with doxorubicin alone, doublet therapy with doxorubicin–ifosfamide was associated with a modestly increased RR at the cost of a higher rate of febrile neutropenia, but no mOS benefit[6,28]. Furthermore, ifosfamide variations developed in the hope of reducing the side effects from metabolites have produced disappointing results[29,30].

The lone trial to demonstrate improved overall survival was the phase IB/II trial that compared olaratumab–doxorubicin with doxorubicin alone[16]. Unfortunately, that result was not replicated in a large phase III study[8]. With respect to anthracycline-sparing regimens, no difference in mPFS or mOS for any subtype of STS was observed in a comparison of first-line gemcitabine–docetaxel with doxorubicin alone; however, quality of life was better for patients treated with doxorubicin alone[17].

Beyond First Line

Upon disease progression, trials have attempted to exploit novel doublets or mechanisms of action (Table II), but mOS and mPFS results have both remained modest. Only eribulin[38,40], gemcitabine–docetaxel[32], and gemcitabine–dacarbazine[33] have been associated with a mOS benefit in doxorubicin-treated patients. Specifically, compared with dacarbazine, eribulin[38,40] demonstrated a benefit in mOS, but not in mPFS, for patients with LMS or LPS—a result that was likely driven by the dedifferentiated LPS subgroup[40]. Notably, a number of studies have compared novel agents with a backbone of dacarbazine, which showed activity in STS in a single-arm phase II study[41,47].

Interestingly, tyrosine kinase inhibitors seem to be associated with an improvement in mPFS, but not mOS. A phase II trial of regorafenib[37,39] and a phase III trial of pazopanib[34], both using a placebo comparator in non-adipocytic sarcomas, and a phase III trial of trabectedin compared with dacarbazine[36] in patients with LMS or LPS, all showed significantly prolonged mPFS (in the order of months), but not mOS.

Immunotherapy

To date, two studies of immunotherapy have been conducted in patients with STS[48,49,a]. The SARC028 study explored the use of pembrolizumab in patients with STS and bone sarcoma after up to 3 prior lines of therapy. The overall RR was 18% (7 of 40 patients), but was likely driven by patients having

TABLE I Selected randomized controlled trials for first-line treatment including doxorubicin

Reference	Study phase	Pts *(n)*	Study arms	RR (%)	CBR (%)	mPFS[a] (months)	mOS (months)
Bramwell *et al.,* 2003[6]	Systematic review	2281	Doxorubicin	16–27	NR	NR	7.7–12
Kalofonos *et al.,* 2004[9]	II	30	Doxorubicin 25 mg/m^2 days 1–3 and cisplatin 100 mg/m^2 day 1	16.7	70	6	11.5
Demetri *et al.,* 2012[10]	I/II	86	Doxorubicin 75 mg/m^2 day 1	24	93	6.4	21.6
			Doxorubicin 75 mg/m^2 and conatumumab 15 mg/kg day 1	20	72	5.6	18.2
Blay *et al.,* 2014[11]	III[b]	121	Doxorubicin 75 mg/m^2 day 1 OR Doxorubicin 60 mg/m^2 day 1 and ifosfamide 6–9 g/m^2 day 1 (37%)	45.9	86.5	8.3	27.3
			Trabectedin 1.5 mg/m^2 day 1	37.3	82.4	18.8	38.9
Gelderblom *et al.,* 2014[12]	II	118	Doxorubicin 75 mg/m^2 day 1	22.2	27.8	NR	NR
			Brostallicin 10 mg/m^2 day 1	3.9	6.5	NR	NR
Judson *et al.,* 2014[13]	III	228	Doxorubicin 75 mg/m^2 day 1	14	59.6	4.6	12.8
			Doxorubicin 75 mg/m^2 day 1 and ifosfamide 10 g/m^2 over days 1–4	26	76.6	7.4	14.3
Bui-Nguyen *et al.,* 2015[14]	IIB	133	Doxorubicin 75 mg/m^2 day 1	25.6	62.8	5.5	NR
			Trabectedin 1.3 mg/m^2 day 1 (3 h)	14.8	55.3	2.8	NR
			Trabectedin 1.5 mg/m^2 day 1 (24 h)	4.7	62.8	3.1	NR
Martin-Broto 2016[15]	II	115	Doxorubicin 75 mg/m^2 day 1	NR	NR	5.5[c]	NR
			Doxorubicin 75 mg/m^2 day 1 and trabectedin 1.1 mg/m^2 day 1	NR	NR	5.7	NR
Tap *et al.,* 2016[16]	II	148	Doxorubicin 75 mg/m^2 day 1	11.9	62.7	4.1	26.5[d]
			Doxorubicin 75 mg/m^2 day 1 and olaratumab 15 mg/kg days 1, 8	18.2	77.3	6.6	14.7[d]
Seddon *et al.,* 2017[17]	III	256	Doxorubicin 75 mg/m^2 day 1	19	72	5.4	17.6
			Gemcitabine 675 mg/m^2 days 1, 8 and docetaxel 75 mg/m^2 day 1	20	75	5.4	15.5[e]
Tap *et al.,* 2019[7] Eli Lilly and Company[8]	III	485	Doxorubicin 75 mg/m^2 day 1	NA	NA	6.8	20.4
			Doxorubicin 75 mg/m^2 day 1 and olaratumab 15 mg/kg days 1 and 8	NA	NA	5.4	19.7

[a] Included studies did not consistently report PFS, and PFS was not included in the final outcomes for the systematic review.
[b] Only translocation-related sarcoma, mostly myxoid or round-cell liposarcoma.
[c] Stopped for futility.
[d] Statistically significant.
[e] Reduced quality of life reported in patients receiving docetaxel–gemcitabine.
Pts = patients; RR = response rate; CBR = clinical benefit rate; mPFS = median progression-free survival; mOS = median overall survival; NR = not reported; NA = not available at time of publication.

the STS subtypes UPS (RR: 40%; 4 of 10) and LPS (RR: 20%; 2 of 10)[48]. To further explore those subtypes, 30 additional patients have been enrolled onto each arm, with results awaited (NCT02301039 at https://ClinicalTrials.gov/). Nivolumab as a single agent demonstrated a modest 5% RR[49]. However, the combination of ipilimumab–nivolumab in patients having received at least 1 prior line of therapy demonstrated a 16% RR (6 of 38 patients: 1 uterine LMS, 1 non-uterine LMS, 1 myxofibrosarcoma, 2 UPS, 1 angiosarcoma)[49].

DISCUSSION

Despite an increase in the number of studies and systemic therapies developed, doxorubicin-based chemotherapy remains the backbone of first-line systemic treatment for advanced STS. Although the MOS is similar with first-line gemcitabine–docetaxel and with doxorubicin alone, patients receiving the combination therapy experience reduced quality of life[17], making gemcitabine–docetaxel a less attractive first-line option. Otherwise, first-line doublet

TABLE II Selected randomized controlled trials beyond first line treatment

Reference	Study phase	Pts *(n)*	Study arms	RR (%)	CBR (%)	mPFS (months)	mOS (months)
Comparative trials							
Bramwell *et al.,* 1987[31]	II	171	Cyclophosphamide 1.5 g/m^2	7.5	41.7	NR	NR
			Ifosfamide 5 g/m^2	17.6	57.3	NR	NR
Maki *et al.,* 2007[32]	II	122	Gemcitabine 1200 mg/m^2 days 1, 8	8	27	3	11.5[a]
			Gemcitabine 1200 mg/m^2 days 1, 8 and docetaxel 100 mg/m^2 day 1	17	32	6.2	17.9[a]
García-del-Muro *et al.,* 2011[33]	II	113	Dacarbazine 1800 mg/m^2 every 3 weeks	4	25	2[a]	8.2[a]
			Dacarbazine 500 mg/m^2 day 1 and gemcitabine 1800 g/m^2 day 1 every 2 weeks	12	49	4.2[a]	16.8[a]
Van der Graaf *et al.,* 2012[34]	III	372	Placebo (no crossover)	0	38	1.6[a]	10.7
			Oral pazopanib 800 mg daily	6	73	4.6[a]	12.5
Blay *et al.,* 2015[35]	III	355	Cisplatin 75 mg/m^2 day 1	1	36	1.41	9.33
			Cisplatin 75 mg/m^2 and ombrabulin 25 mg/m^2 day 1	4	47	1.54	11.43
Demetri *et al.,* 2016[36]	III	518[b]	Dacarbazine 1000 mg/m^2 day 1	6.9	19	1.5[a]	12.4
			Trabectedin 1.5 mg/m^2 day 1	9.9	34	4.2[a]	12.9
Mir *et al.,* 2016[37]	II	43 LPS	Placebo (could cross over)	0	43	1.7	8.8
			Oral regorafenib 160 mg daily for 21 days; 7 days off	0	57	1.1	4.7
		56 LMS	Placebo (could cross over)	4	58	1.8	9.1
			Oral regorafenib 160 mg daily for 21 days; 7 days off	0	86	3.7	21
		27 SyS	Placebo (could cross over)	0	22	1.0	6.7
			Oral regorafenib 160 mg daily for 21 days; 7 days off	8	85	5.6	13.4
		56 Other	Placebo (could cross over)	0	34	1.0	9.5
			Oral regorafenib 160 mg daily for 21 days; 7 days off	11	78	2.9	12.1
Schöffski *et al.,* 2016[38]	III	452[b]	Dacarbazine 850–1200 mg/m^2 day 1	5	48	2.6	11.5[a]
			Eribulin 1.4 mg/m^2 days 1, 8	4	46	2.6	13.5[a]
Berry *et al.,* 2017[39]	II	60[c]	Placebo (could cross over)	NR	NR	1.0[a]	9.0
			Oral regorafenib 160 mg daily for 21 days; 7 days off	NR	NR	4.0[a]	13.4
Demetri *et al.,* 2017[40]	III	143[d]	Dacarbazine 850–1200 mg/m^2 day 1	0	44.4	1.7	8.4[a]
			Eribulin 1.4 mg/m^2 days 1, 8	0.4	65.2	2.9	15.6[a]
Selected single-agent trials							
Buesa *et al.,* 1991[41]	II	44	Dacarbazine 1200 mg/m^2 day 1 every 3 weeks	18	36.3	NR	NR
Nielsen 2000[27]	II	124	Ifosfamide 12 g/m^2	16	48	3.5	12.7
Talbot *et al.,* 2003[42]	II	26	Temozolomide	15.4	26.9	2	13.2
George *et al.,* 2009[43]	II	48	Oral sunitinib 37.5 mg daily	2	14	NR	NR
Maki *et al.,* 2009[44]	II	144	Oral sorafenib 400 mg twice daily	6	68	3.2	14.3[e]
Luo *et al.,* 2015[45]	II	26	Gemcitabine 1000 mg/m^2 days 1, 8; vincristine 1.4 mg/m^2 day 1; and cisplatin 25 mg/m^2 days 1–3	23	65.3	4.8	15
Subbiah *et al.,* 2018[46]	IB/II	25	Pazopanib 800 mg and oral trametinib 2 mg daily	8	56	2.27	9

[a] Statistically significant.
[b] Liposarcoma or leiomyosarcoma only
[c] Included only non-adipocytic sarcoma, unplanned analysis.
[d] Planned subgroup analysis of liposarcoma cohort in Demetri *et al.,* 2016[36].
[e] Mostly driven by the angiosarcoma cohort.
RR = response rate; CBR = clinical benefit rate; mPFS = median progression-free survival; mOS = median overall survival; NR = not reported; LPS = liposarcoma; LMS = leiomyosarcoma; SyS = synovial sarcoma.

chemotherapy has generally been shown to increase the RR, but not the mPFS or mOS[6] (Table I). The phase IB/II results for olaratumab–doxorubicin[16] initially suggested an impressive mOS benefit, resulting in accelerated conditional approval; however, the larger phase III study of that combination compared with doxorubicin alone was negative[7]. The difference in mOS might have been attributable to overperformance in the doxorubicin-alone arm or to the proportions of the heterogeneous STS population captured in each study being different. Which, if any, subtype of STS might respond best to the combination remains an open question.

However, the foregoing results do reinforce the trend seen in Table I that the mOS for first-line doxorubicin-only treatment in STS is indeed increasing over time, but that the RR and progression-free survival have generally remained stagnant. Those observations might be attributable to additional evidence and to an increase in the agents available for second-line therapy, coupled with a better understanding of subtype-directed therapy[50]. Furthermore, supportive care in oncology has improved over time, which could account for improved outcomes such as a quality of life[51].

Although the present review focuses on systemic therapy, patients with advanced STS receive multidisciplinary care from radiation and surgical oncologists. More frequent use of metastasectomy and radiation (specifically, stereotactic ablative radiation therapy) in carefully selected patients with a long disease-free interval or long-interval disease stability might also explain improved outcomes for patients over time[52,53].

Single-agent doxorubicin remains the agent of choice in the first-line treatment of most advanced STS; however, in carefully selected patients (such as those with borderline resectable tumours, rapid tumour growth, and a deteriorating performance status or a tumour near critical anatomic structures), doxorubicin–ifosfamide might be considered as first-line treatment because of its higher RR (Figure 3). In patients with cardiac comorbidities, clinicians could consider using liposomal doxorubicin or gemcitabine–docetaxel in the first line to avoid potential worsening of underlying cardiac dysfunction.

After treatment with anthracyclines, subtype becomes an important consideration. Based on our scoping review, we propose an algorithm (Figure 3). Outside the scope of our review, subtype-directed therapy for rare histologies such as alveolar soft-part sarcoma, perivascular epithelioid-cell neoplasms, and angiosarcoma is well summarized in other published review articles[50]. For patients with LMS (and to a greater extent LPS), eribulin is an active therapy that improves mOS[38,40]. Although activity of gemcitabine–docetaxel was initially reported in a phase II trial that included only patients with LMS[54], a preplanned subgroup analysis from the GeDDiS trial[17] showed no evidence of a differential benefit based on subtype, including uterine compared with non-uterine LMS compared with other histologies. Thus, gemcitabine–docetaxel is an established treatment for patients with multiple subtypes of STS after failure of anthracyclines. The smaller phase II study of dacarbazine–gemcitabine in previously treated patients

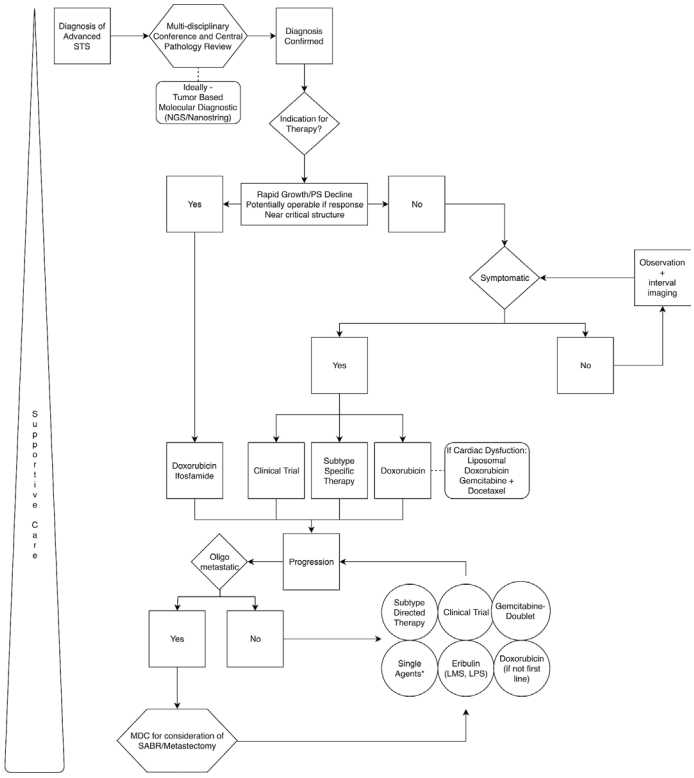

FIGURE 3 Proposed treatment algorithm for advanced soft-tissue sarcoma (STS). [a]Dacarbazine, gemcitabine, pazopanib, trabectedin. NGS = next-generation sequencing; PS = performance status; LMS = leiomyosarcoma; LPS = liposarcoma; MDC = multidisciplinary conference.

with STS showed a significant mOS benefit, but the primary outcome of the study was the progression-free survival rate at 3 months. Given that the larger phase III study of gemcitabine–docetaxel represents a higher level of evidence, we favour use of that gemcitabine doublet unless the patient has a contraindication to taxanes. Although randomized data are limited, dacarbazine is often included as a backbone for systemic therapy beyond anthracyclines[33,36,38,40] and can be considered an option for patients who are fit enough to receive systemic therapy after doublets and for whom subtype-specific therapy has been exhausted.

Delaying the need to switch therapies is an important outcome, but must be balanced when a switch does not translate into a change in mOS. Pazopanib[34], regorafenib[39], and trabectedin[36] are associated only with improved mPFS, not mOS. Although establishing a large trial of heterogeneous STS is challenging, the question of whether those therapies might benefit a specific subgroup remains open.

A large retrospective analysis from the European Organisation for Research and Treatment of Cancer suggested that, in patients with STS, lack of progression is an important predictor of mOS[55]. However, that hypothesis has not held true in large phase III studies that have shown improvement in mPFS, but not mOS[34,36]—perhaps because of difficulty in interpreting imaging for patients with STS. The size of tumours is often non-uniform, which makes interpretation according to the Response Evaluation Criteria in Solid Tumors difficult. Similarly, response might be better reflected by qualitative change in imaging rather than by size alone[56]. Furthermore, mPFS is critically affected by the design of follow-up imaging, which can influence results[57].

Another interesting outcome to consider with pazopanib, regorafenib, and trabectedin might be time to second progression, which might help with the sequencing of available agents and represent a clinically meaningful outcome for patients.

Looking beyond cytotoxic or targeted therapy, novel mechanisms of systemic therapy such as immunotherapy have changed the landscape of treatment for a variety of tumour groups[58]. Although early results suggest that immunotherapy could be effective in certain STS subtypes such as UPS and LPS[48,49], larger cohorts with longer follow-up are required to better understand the true clinical benefit of those agents for patients with STS.

The rarity of STS and its subtypes generally precludes large subtype-specific randomized trials. However, within the STS subtypes, heterogeneity can be seen in terms of grade, chemoresponsiveness, and prognosis. That heterogeneity often cannot be adequately teased out in large STS trials that group multiple STS histologies having potentially dissimilar biology[50]. Despite histologic heterogeneity, RRs might vary, potentially contributing to the differing results seen in the phase II compared with the phase III trial of olaratumab–doxorubicin[8]. Inclusion criteria such as disease progression within 3 months of enrolment, grade, subtype, and mandated central pathology review should all be carefully considered in attempting to reduce heterogeneity. Alternatively, subtype-specific trials have been successful in the past[38,59] and could provide robust evidence to inform practice and remove the inherent heterogeneity when many STS subtypes are included in a trial.

Currently, clinicians might be more comfortable applying the results of large, randomized STS trials to patients with common STS histologies such as LPS or LMS; for uncommon subtypes, uncertainty remains, highlighting the continued importance of real-world data from retrospective cohorts of patients with rare STS subtypes as the best evidence to direct therapy. Active trials are generally focusing on small molecules in selected sarcoma subtypes[56–58]. The focus on subtype-directed therapy has led to the emergence of platforms such as NanoString fusion assays (NanoString Technologies, Seattle, WA, U.S.A.), which can help to confirm the STS subtype, potentially helping to tailor systemic treatment[60]. For example, *TRK* fusions are present in at least 0.4%[61] of the unselected population with sarcoma, but are pathognomonic for infantile fibrosarcoma[62]. Larotrectinib, a potent pan-TRK inhibitor has been associated with an impressive 75% RR in adults and children with *TRK* fusions[63].

Currently, sequencing tumours in an attempt to identify driver mutations and to personalize care is a growing trend in all tumour types. Sequencing is being done quite frequently in sarcoma as well, although the somatic mutation burden in STS is low relative to that in other tumours[64]. Next-generation sequencing studies in patients with STS show a 41% actionable mutation rate[65]. Importantly, to better understand whether tumour-directed therapy will translate to improved mOS, a number of basket trials matching known actionable mutations to active systemic therapy are enrolling patients with various tumour types (see NCT03297606 and NCT02534649 at https://ClinicalTrials.gov/).

We performed a broad scoping review with the aim to include all appropriate and relevant studies. It is important, however, to recognize that our methods do not represent a complete systematic review of the literature. For example, some studies might have been missed, because we included only studies published in English. However, efforts were undertaken to ensure inclusion of key studies for the treatment of advanced STS. Our review focused on randomized or prospective data collection; results from retrospective cohorts of STS patients or specific subtypes were not included.

SUMMARY

Although the number of published studies has increased over time, the most important systemic treatment for advanced STS remains anthracycline-based therapy. For patients treated with first-line doxorubicin, survival has steadily increased over time. However, the selection of optimal systemic therapy after anthracycline-containing regimens remains a challenge, with few agents showing survival benefit. Ongoing studies in immunotherapy, novel chemotherapy combinations, molecular diagnostics, and targeted agents aim to further improve outcomes.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS

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