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REVIEW

Treatment of Adult Soft Tissue Sarcomas: An Overview

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ABSTRACT

Sarcomas are uncommon malignancies accounting for about 1% of all adult malignancies. Sarcomas are a heterogeneous group of tumors which includes more than 100 different subtypes. Surgery is the mainstay therapy for localized disease. In selected patients the combination of surgery with radiotherapy achieves better local control and offers the best chance of cure. Systemic treatment including cytotoxic chemotherapy or targeted therapies remains the mainstay therapy for most patients with advanced disease. There are a wide variety of clinical situations, such that an individualized treatment plan must be defined by a multidisciplinary tumor board. Treatment decisions should take into consideration the histology, site of disease, stage, performance status, treatment goals, and the patient's wishes. The management of patients should be carried out in a center with expertise in the treatment of sarcomas for optimal outcome. This review will cover the different treatment modalities of adult soft tissue sarcomas.

Keywords: Chemotherapy; Radiotherapy; Soft tissue sarcoma; Surgery; Targeted therapy

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INTRODUCTION

Soft tissue sarcomas (STSs) are mesenchymal derived cancers which have more than 100 histological subtypes according to the most recent World Health Organization classification [1]. These tumors are rare and account for less than 1% of all adult malignancies [2]. In the USA 11,930 new cases of STS are diagnosed each year with 4870 deaths [3]. They arise from any part of the body, but the majority occur in the extremities (59.5%) followed by the trunk (17.9%) [4]. The most common histologic subtypes in adults are

undifferentiated unclassified sarcoma, liposarcoma, leiomyosarcoma, synovial sarcoma, and malignant peripheral nerve sheath tumor (MPNST) [1]. Painless mass is the most common clinical presentation. Tumor tends to grow locally along tissue planes, surrounded by a so-called pseudocapsule which contains malignant cells infiltrating adjacent tissues [1]; therefore, the dissection along the pseudocapsule is contraindicated [5]. The presence of distant metastases at the time of initial diagnosis is rare [6]. The most common pattern of spread is via blood, typically to the lung [6]. Lymph node metastases are infrequent (less than 3%) [7], with the exception of certain histologies such as epithelioid sarcoma, rhabdomyosarcoma, angiosarcoma, and clear cell sarcoma [7]. Pretreatment evaluation includes magnetic resonance imaging of the primary site and chest computed tomography [5]. Tumor stage is the most important prognostic factor. The most recent, 7th edition of the American Joint Committee on Cancer (AJCC) system is the most widely used. It incorporates tumor size, depth, lymph node involvement, distant metastases, and histologic grade in determining four stage groups with different outcome [8]. Thus, reported 5-year overall survival (OS) rates for stages I, II, and III were 90%, 81%, and 56%, respectively [8]. In addition to tumor stage, other prognostic factors are anatomic site, histologic subtype, age, and surgical margins [9]. The management of patients with STS requires a multimodality treatment provided by an expert multidisciplinary team working in a reference center or within a reference network [5]. Thereby, clinical practice guidelines recommend referral of all patients with suspected sarcoma to a reference center for appropriate diagnostic and optimal outcome [5]. In fact, Gustafson et al. [10] demonstrated that patients treated at a tumor center have better outcome as compared to patients who were not referred to a tumor center or those who were referred to a tumor center after surgery. In their series local recurrence was 2.4 times higher when patients were treated outside of a reference center and 1.3 times higher if the patients were referred to a tumor center after surgery [10].

The present review covers different treatment modalities for adult STSs based on recent clinical practice guidelines, data from clinical trials, and meta-analysis. We have excluded from this review extraskeletal Ewing sarcoma, embryonal rhabdomyosarcoma, alveolar rhabdomyosarcoma, and gastrointestinal stromal tumors (GIST), as they belong to separate therapeutic approaches. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

TREATMENT OF LOCALIZED DISEASES

Surgery

Surgery is the standard treatment of localized STS [5] and consists of a wide surgical resection, with total en bloc excision of the primary tumor, the biopsy site, and a rim of normal tissues around the tumor [11]. Dissection along the pseudocapsule is strictly prohibited [5]. Resection margins represent the main risk factor for local recurrence [11]. The Union for International Cancer Control (UICC) recommends to report the quality of surgery in STS according to the resection type (R) with R0 as *in sano*, R1 as microscopic residual disease, and R2 as macroscopic residual disease. Resection type should be assessed collegially

by pathologists and surgeons for an accurate estimation of resection margins, since the decision for re-excision or complementary treatment depends on the determination of the quality of surgery [12, 13]. There is no consensus regarding the relevant cutoff of the minimal margin [5]. In general, 1-cm margins are recommended; however, close margins may be necessary in some cases to preserve uninvolved major neurovascular structures [13]. Moreover, narrow margins of resistant anatomical barriers, such as muscular fasciae, periosteum, and epineurium, are likely to be adequate [5].

As regards sarcomas of the extremities, it has been demonstrated that limb-sparing surgery alone or in combination with radiotherapy (RT) in selected patients offers comparable rates of disease control and survival as amputation, as long as wide resection margins are achieved [14–16]. Therefore, primary limb amputation must be avoided in most patients. However, amputation may be the only potentially curative option in some cases including large and extensive tumors which compromise the achievement of a conservative approach with a good functional limb outcome or in case of major complications [17]. Those situations should be carefully assessed by a multidisciplinary team before carrying out amputation.

Because lymph node involvement is uncommon in STS, systematic regional node dissection is not recommended [5]. Node dissection should be performed only if there is evidence of lymph node disease [7]. In this setting, it has been reported that radical lymphadenectomy for isolated regional lymph node metastases provides long-term survival: 46% 5-year survival, with a median survival of 16.3 months versus 4.3 months in patients not treated with lymph node dissection [7]. However, it is unclear if treatment of occult node metastases based on earlier detection of metastatic nodes by sentinel lymph node biopsy or positron emission tomography would improve outcome in histologies with higher frequency of lymph nodes metastasis including epithelioid sarcoma, rhabdomyosarcoma, angiosarcoma, synovial sarcoma, and clear cell sarcoma [18, 19].

Surgery alone with negative margins provides a local control rate close to 93% in a selected subset of patients (superficial and low grade tumors that are 5 cm or less in size, and selected truly intracompartmental tumor) [20, 21]. However, some patients are at high risk of recurrence and will require complementary treatment [22].

Radiotherapy

The benefit of RT as adjuvant treatment to limb-sparing surgery has been initially addressed in comparison with radical surgery. These studies have shown that RT, when combined with conservative surgery, provides similar rates of local control to those achieved with amputation [14]. Since the publication of these results, amputation as a primary therapy has largely been abandoned for most patients [15]. So, with the emergence of RT in the management of STSs, two randomized trials using different modalities of radiation therapy (external beam RT (EBRT) [23] or brachytherapy [24]) have been conducted in order to assess the impact of adjuvant RT on local and systemic recurrence in patients with localized STS (Table 1). The two studies demonstrated that adding RT to limb-sparing surgery reduces the risk of local recurrence by 20–25% when compared to limb-sparing surgery alone without any advantage in OS [23, 24]. The benefit of RT was seen in high-grade and

Table 1 Randomized trials of radiotherapy in localized adult soft tissue sarcomas

Study	*N*	Treatment	Local recurrence	DFS (5 years)	OS (5 years)
Rosenberg et al. [14]	43	LSS + postoperative RT	14.8%	71%	83%
		Amputation	0%	78%	88%
			$P = 0.06$	$P = 0.75$	$P = 0.99$
Yang et al. [23]	141	LSS + postoperative RT	0.01%	NR	75%[b]
		LSS	23.9%	NR	74%[b]
			$P = 0.0001$		$P = 0.71$
Pisters et al. [24]	119	Surgery + brachytherapy	16.7%	83%[a]	84%[c]
		Surgery	29%	76%[a]	81%[c]
			$P = 0.04$	$P = 0.60$	$P = 0.65$
O'Sullivan et al. [31]	190	Preoperative RT (50 Gy)	7%	58%	73%
		Postoperative RT (66 Gy)	8%	59%	67%
			$P = 0.48$	$P = 0.48$	$P = 0.48$

DFS disease-free survival, *LSS* limb-sparing surgery, *NR* not reported, *OS* overall survival, *RT* radiotherapy

[a] 5-year distant metastasis-free survival

[b] 10-year overall survival in high-grade STS

[c] 5-year disease-specific survival

low-grade tumors in one trial [23], whereas it was limited to high-grade tumors in the other one [24]. The identification of patients who require adjuvant RT is mandatory. Several predictor factors of local recurrence have been identified. The most important factor is surgical margins [25]. Patients with positive margins are at increased risk of local recurrence. A relative risk (RR) of 2.9 [95% confidence interval (CI) 1.8–4.6] has been reported in patients with positive margins who did not receive adjuvant treatment [26]. Positive surgical margins have been associated with local recurrence risk even in patients treated with combined surgery and RT [9]. Re-excision seems to be the best option for favorable outcome in patients with marginal resection. Zagars et al. [27] reported local control rates of 85%, 85%, and 82% at 5, 10, and 15 years, respectively, for patients who underwent re-resection versus 78%, 73%, and 73%, respectively, for patients who did not undergo re-resection [27]. Therefore, re-excision must be strongly considered in case of R2 or R1 resections, if adequate margins can be achieved without major morbidity [5, 13].

Postoperative RT improves local control in patients with marginal excisions and in those with residual tumor cells after re-excision. The 10-year local recurrence rates for patients treated with surgery alone and patients treated with combined surgery and RT was 17% (95% CI 8–32%) versus 53% (95% CI 25–75%), respectively ($P = 0.005$), in patients with marginal resection and 84% in the RT group versus 37% in the no-RT group ($P = 0.001$) in patients with residual cells after re-excision [28].

Several independent adverse prognostic factors for local recurrence have been reported

in retrospective series and population-based registries [8, 9, 25, 29]. The most relevant are recurrent disease at presentation, histology, age, tumor grade, deep location, and tumor size.

A prospective nomogram which aims to estimate the risk of local recurrence for an individual patient has been established recently. The nomogram was developed from a prospective sarcoma database including 684 patients with primary, non-metastatic, extremity STS treated with limb-sparing surgery alone without adjuvant therapy. It includes five independent predictor factors of relapse: age, size, surgical margin, grade, and histology. The nomogram is useful to quantify individual 3- and 5-year risk of local recurrence; however, there is insufficient evidence to support routine use of this nomogram for clinical decision-making [22].

The recent clinical practice guidelines recommend radiation therapy as the standard treatment of lesions that are high grade, deep, and larger than 5 cm [5, 13]. There is no consensus regarding the indication of adjuvant RT for selected cases, namely STSs that are low or high grade, superficial, and larger than 5 cm; low grade, deep, and smaller than 5 cm; or low grade, deep, and larger than 5 cm. So the decision should be discussed in a multidisciplinary setting and must be shared with the patient [5]. Most high-grade lesions that are deep and smaller than 5 cm should be treated with surgery followed by radiation therapy with exceptions to be discussed in a multidisciplinary board [5, 13].

RT can be administered preoperatively or postoperatively [5]. A phase III trial comparing these two modalities reported similar efficacy in terms of local control and survival [30]. After a median follow-up of 6.9 years, over 90% of patients are controlled locally, with similar rates of progression-free survival (PFS) and OS [31]. However, the two approaches differ substantially in their side effects. Acute wound complications were significantly more common with preoperative RT (35%) as compared to postoperative RT (17%; 95% CI 5–30%; $P = 0.01$). Wound healing was affected by the extent of the surgery and anatomical site of the tumor [30]. Postoperative RT induces higher rates of late complications including edema, fibrosis, and joint stiffness, which are often irreversible and adversely affect functional outcome [30]. The differences in the morbidity and functional outcome between these two approaches could be related not only to the timing of RT but also to the larger radiation field and the higher doses (66 versus 50 Gy) associated with postoperative RT [30].

The optimal timing of radiation therapy has yet to be defined. However, because of the lower rates of long-term complications and the better functional outcome reported in O'Sullivan et al.'s [30] trial there is a current trend toward preoperative RT, especially when the dose and field size are important issues. Nevertheless, postoperative RT might be preferable if severe wound-healing complications are anticipated.

Modern RT techniques such as image-guided RT and intensity-modulated RT treatment might reduce the risk of acute wound-healing problems when preoperative RT is administered and the risk of long-term side effects when postoperative RT is given [32].

The treatment should be individualized and the best option should be discussed in a multidisciplinary tumor board. A total dose of 50 Gy in 1.8- to 2-Gy fractions is recommended, possibly with a boost up to 66 Gy, depending on presentation and resection margins [5].

Brachytherapy is another modality of RT in which a radiation source is placed inside the targeted area. It delivers high dose of radiation to the tumor while minimizing the dose to

surrounding normal tissues [21]. Postoperative brachytherapy (45 Gy) reduces recurrence in high-grade STSs by 23% [21]. There is no randomized trial comparing brachytherapy to EBRT. Further studies are needed to identify patients for whom brachytherapy may be preferred.

Chemotherapy

In spite of effective local treatment, 25% of patients will develop distant metastases [9, 33]. Thus an effective systemic treatment to eradicate micro-metastases is strongly warranted. Over 20 randomized trials and two meta-analyses have investigated the role of adjuvant chemotherapy in localized adult STS (Table 2). Study results were conflicting. Thus, the role of adjuvant chemotherapy in patients undergoing local therapy remains unclear. The first meta-analysis by the Sarcoma Meta-analysis Collaboration published in 1997 found an improvement in local and distant recurrence-free intervals in the chemotherapy group, but no benefit in terms of OS [34]. However in the subset of patients with sarcomas of the extremities there was a statistically significant benefit in terms of OS in favor of adjuvant chemotherapy [hazard ratio (HR) for death = 0.80; $P = 0.029$] [34]. This meta-analysis includes early randomized trials which used suboptimal adjuvant regimens. An updated meta-analysis including four additional new trials which used optimal dosages of doxorubicin in addition to ifosfamide confirms the limited benefit of adjuvant chemotherapy in terms of local recurrence, distant recurrence, and overall recurrence [35]. However, in contrast to the earlier meta-analysis, adjuvant chemotherapy yielded improvement in OS with an HR of 0.77 (95% CI 0.64–0.93; $P = 0.01$). The benefit is further improved with regimens combining ifosfamide with doxorubicin with an absolute risk reduction of 11% (95% CI 3–19%; $P = 0.01$) or a 30% versus 41% risk of death [35]. However, a survival benefit could not be found in the most recent and largest study of the European Organization for Research and Treatment of Cancer (EORTC) which was not included in the updated meta-analysis [36]. The trial randomly assigned 351 patients to receive either adjuvant chemotherapy (doxorubicin at 75 mg/m^2 with ifosfamide at 5 g/m^2) or no additional systemic chemotherapy following surgery. The lack of efficacy might be influenced by the inclusion of patients with non-extremity sarcomas (33%), low- and intermediate-grade tumors (55%), and of tumors smaller than 10 cm (63%), as well as by the low dose of ifosfamide. Therefore, no definitive conclusions can be drawn. A pooled analysis combining individual patient data from this trial with another large randomized adjuvant trial found no survival benefit of adjuvant chemotherapy except in patients with marginal resection (Table 2) [37].

It is unknown whether adjuvant chemotherapy may be particularly beneficial in specific chemosensitive histologies such as myxoid, round cell liposarcoma [38] and synovial sarcoma [39]. Available data from retrospective series suggest a potential benefit of adjuvant chemotherapy in selected histologies [40, 41]; however, neither randomized clinical trials nor meta-analyses have confirmed this finding [34, 35, 37].

On the basis of these data, adjuvant chemotherapy is not standard treatment in adult-type STS. It can be proposed as an option in high-risk individual patients (with a high-grade, deep tumor larger than 5 cm), but should not be considered in histological subtypes known to be chemoresistant [5].

Table 2 Meta-analysis of adjuvant chemotherapy in adult soft tissue sarcomas

Study	No. of trials	No. of patients	Regimen	Doxorubicin and ifosfamide dosage	Local recurrence	Distant recurrence	Overall recurrence	Overall survival
1997 sarcoma meta-analysis collaboration [34]	14	1568	Doxorubicin alone ($n = 6$) Doxorubicin + other chemotherapy drugs ($n = 7$) Doxorubicin + ifosfamide + DTIC ($n = 1$)	Doxorubicin: 50–70 mg/m^2 per cycle Ifosfamide: 1500 mg/m^2 per cycle	HR = 0.73 (95% CI 0.56–0.94) $P = 0.016$	HR = 0.70 (95% CI 0.57–0.85) $P = 0.0003$	HR = 0.75 (95% CI 0.64–0.87) $P = 0.0001$	HR = 0.89 (95% CI 0.76–1.03) $P = 0.12$
2008 updated meta-analysis [35]	18	1953	Doxorubicin alone ($n = 6$) Doxorubicin + other chemotherapy drugs ($n = 7$) Doxorubicin + ifosfamide ($n = 5$)	Doxorubicin: 50–70 mg/m^2 per cycle Ifosfamide: 1500–5000 mg/m^2 per cycle	OR = 0.73 (95% CI 0.56–0.94) $P = 0.02$)	OR = 0.67 (95% CI 0.56–0.82) $P = 0.0001$	OR = 0.67 (95% CI 0.56–0.82) $P = 0.0001$	HR = 0.77 (95% CI 0.64–0.93) $P = 0.01$
Pooled analysis of EORTC-STBSG clinical trials [37]	2	819	Doxorubicin + other chemotherapy drugs ($n = 1$) Doxorubicin + ifosfamide ($n = 1$)	Doxorubicin: 50–75 mg/m^2 per cycle Ifosfamide: 5 g/m^2	NR	NR	HR = 0.74 (95% CI 0.60–0.92) $P = 0.0056$	NS

CI confidence interval, *HR* hazard ratio, *NR* not reported, *NS* not significant, *OR* odds ratio

A new therapeutic approach consisting of regional hyperthermia in addition to systemic chemotherapy has been investigated in a large randomized phase III trial [42]. Patients with localized high-risk STS (G2–3, deep, at least 5 cm) were randomly assigned to receive either neoadjuvant chemotherapy alone or combined with regional hyperthermia in addition to local therapy. This approach was associated with a local PFS advantage (HR = 0.58; 95% CI 0.41–0.83) and disease-free survival benefit (HR = 0.70; 95% CI 0.54–0.92]). Response rate was higher in the group with regional hyperthermia 28.8% versus 12.7% in the group that received chemotherapy alone ($P = 0.002$). OS was better in the combined therapy group with an HR = 0.66 (95% CI 0.45–0.98; $P = 0.038$) [43]. Thus, this therapeutic strategy offers a new therapeutic option for patients with high-risk STS including abdominal or retroperitoneal location [5, 42, 43].

PRIMARY LOCALLY ADVANCED SOFT TISSUE SARCOMAS

For patients with unresectable primary locally advanced tumors, combined therapeutic modalities should be considered. The main objective of combined therapeutic modalities is to ovoid mutilating surgery, to improve local control, OS, and minimize sequelae.

Isolated limb perfusion (ILP) is the most investigated approach in this setting. This technique provides high concentration of antineoplastic agents locally without exposing the patient to high systemic levels of the drug by isolating the vasculature of a limb temporarily. ILP uses high doses of tumor necrosis factor alpha (TNFα) and melphalan with or without interferon and is usually associated with local hyperthermia. Several groups have reported their experience with upfront ILP. Results were consistent among all these studies. The overall response rate was greater than 70% and limb salvage rate about 80% [44–48].

Regional hyperthermia in addition to systemic chemotherapy might be a good alternative. A phase II trial which was conducted in locally advanced primary or recurrent STS found an overall response rate of 17% with a high rate of histological response and a better outcome in patients responding to the combined approach [49]. Furthermore, a subgroup analysis of the most recent phase III trial found better local PFS in patients with very large tumors (larger than 12 cm) in the chemotherapy plus regional hyperthermia group as compared with patients receiving chemotherapy alone [43].

Note that both regional hyperthermia and ILP are not widely available because of the highly technical procedures required for these approaches.

Preoperative chemoradiotherapy represents another option to manage locally advanced STS [5] and available data suggest that it can be administered safely [50]. Concomitant chemoradiotherapy with low dose doxorubicin provided 67% objective response (11% complete and 56% partial response) in 115 patients. Thirty-nine responders underwent surgery including 24 primary tumors and 15 relapses. The median survival was 29 and 50 months in responder patients [51]. Limited data exist regarding the concomitant use of ifosfamide with RT. A retrospective series of 43 patients has reported promising results that need to be confirmed by further studies [52]. Concurrent multi-agent chemotherapy (doxorubicin, ifosfamide, and dacarbazine) with RT was assessed in the Radiation Therapy

Oncology Group (RTOG) study involving 66 patients. The 5-year rates of distant and locoregional failure (including amputation) were 28% and 22%, respectively. Five-year OS was 71%. But serious treatment-related toxicities were experienced in 83% of cases; 11% had major postoperative complications, and three patients experienced fatal grade 5 toxicities [53].

The benefit of neoadjuvant chemotherapy alone in the management of locally advanced STS is uncertain. In fact, it is unknown if upfront systemic chemotherapy may convert an initially unresectable tumor to a resectable one or if it may improve the rate of margin-negative resection. The single phase II trial assessing the impact of preoperative systemic chemotherapy in high-risk STS (tumors of at least 8 cm, high grade, locally recurrent, inadequate surgery) failed to show any benefit [54]. This option could be considered in chemosensitive STS using multi-agent chemotherapy with anthracycline, ifosfamide with or without dacarbazine given to the higher response rate achieved by these protocols [55, 56].

In the absence of randomized controlled trials to define the most effective strategy to manage locally advanced STS, there is no consensus among reference centers and therapeutic options are usually influenced by the availability of technical equipment and the institutional experience.

LOCALLY RECURRENT SOFT TISSUE SARCOMAS

About 15% of patients with STS will develop a local relapse in spite of effective local therapy for the primary lesion [57, 58]. Local recurrence occurs mostly within the first 2 years [57]. The outcome is poorer as compared to primary cases because of the increased risk of distant failure [59]. Wide surgical resection is the cornerstone of treatment [5]. Radiation therapy improves local control and should be considered [5, 13]. However, achieving adequate surgical margins, salvage of the limb, and re-irradiation are often an issue in patients with recurrent STS.

Functional conservative management is always preferable but not always possible. In some cases, amputation remains the only potentially curative option, especially in previously irradiated patients.

In patients who had prior RT for their primary tumor, Indelicato et al. [60]. reported high morbidity with re-irradiation with 50% of serious complications requiring either reoperation or leading to permanent functional impairment. Brachytherapy can be an alternative for patients who had prior RT, since it provides superior rates of local control with acceptable complications [61].

Other options including neoadjuvant systemic chemotherapy or regional chemotherapy can be discussed. In fact, promising results have been reported with ILP in the management of recurrent disease. A report of 26 patients with recurrent STS, in the irradiated field, treated with TNFα-based ILP has shown a response rate of 70%. Amputation was avoided in 17 patients (65%). Local recurrence rate was 45% in patients with multiple tumors and 27% in patients with a single tumor [62]. Regional hyperthermia combined with systemic chemotherapy might also be a good option in patients with recurrent STS. A subgroup analysis demonstrated that this new intervention results in significantly better local PFS compared with systemic neoadjuvant chemotherapy alone [43]. Further trials are needed to assess the potential benefit and the safety profile of this new

treatment in this specific population of patients.

TREATMENT OF METASTATIC SOFT TISSUE SARCOMAS

Management of metastatic STS is a challenging problem. Treatment is essentially palliative and the potential for cure decreases drastically. The reported median OS is about 12–18 months [63, 64]. However, about 5–8% of patients are alive progression-free 5 years after the initial diagnosis of metastasis, and most will not relapse later [65]. Chemotherapy is the mainstay of treatment in the metastatic setting. However, surgery of metastatic lesions if feasible should be offered since it provides long-term survival [66]. Reported median survival after complete excision of isolated lung metastases is 33–35 months versus 11–13 months in patients with non-surgical treatment [66, 67]. Patients with extrapulmonary metastases can also achieve significant long-term survival when a complete resection is possible for both the pulmonary and extrapulmonary metastases [66].

Unfortunately most patients are not amenable to ablative approaches. In these instances, treatment is palliative and is based on systemic chemotherapy.

Chemotherapy

Doxorubicin alone at the dose of 75 mg/m^2 once every 3 weeks is considered the treatment of choice in the first-line setting. It achieves a response rate of 10–25% and a median survival in the range of 1 year [63, 64]. It is the most effective chemotherapeutic agent available against multiple histological subtypes [68]. The maximum cumulative dose that should be administered should not extend 550 mg/m^2 to avoid cumulative cardiotoxicity. Pegylated liposomal doxorubicin has similar efficacy with an improved toxicity profile as compared to doxorubicin in a phase II trial. However response rates were lower than normally expected (ca. 10%), probably because of the high proportion of GIST in this study population [69].

The second most commonly used drug in soft tissue sarcoma is ifosfamide. Used as monotherapy, ifosfamide results in response rates of 20–25% in non-pretreated patients [70–72]. Ifosfamide has higher activity in synovial sarcoma and less antitumor activity in leiomyosarcoma [73]. The response rate to ifosfamide is both dose- and schedule-dependent [72]. A randomized phase II study comparing standard-dose ifosfamide 5 g/m^2 over 24 h versus ifosfamide 3 g/m^2 daily for 3 days reported a response rate of 10% for the lower-dose treatment and 25% for the higher dose [71]. Therefore, the most commonly used scheme is 3 g/m^2 ifosfamide administered on days 1, 2, and 3, repeated every 3 weeks. A role for high-dose ifosfamide (14–18 mg/m^2) has been suggested in the treatment of metastatic synovial sarcoma [74].

A head-to-head comparison of doxorubicin and ifosfamide in first-line treatment for patients with advanced and/or metastatic soft tissue sarcoma found no differences in PFS, OS, or response rates. However, grade 4 toxicities were more frequent in the ifosfamide arms [75]. This finding supports the use of single-agent doxorubicin as the treatment of choice in metastatic STS, though ifosfamide is a reasonable alternative if patients cannot be treated with an anthracycline initially.

Multi-agent chemotherapy with doxorubicin plus ifosfamide in first-line treatment of metastatic STS results in higher overall

response rate (26.5% versus 13.6%), but without survival advantage over single agent doxorubicin [64]. Therefore, combination therapy may be considered only when a tumor response is felt to be potentially advantageous [5].

Ifosfamide may be used after failure of anthracycline-based chemotherapy in patients who did not progress on it previously [5, 13]. The median survival of patients exposed to ifosfamide in second-line treatment after doxorubicin failure is in the range of 35–45 weeks with a median time-to-progression of 6–14 weeks [70, 71]. For patients who have already received standard-dose ifosfamide, high-dose ifosfamide is a reasonable option [76, 77].

Other conventional cytotoxic drugs such as dacarbazine [78, 79], temozolomide [80], pacliatxel [81], docetaxel [82–84], gemcitabine [82, 83], and carboplatin [85] have demonstrated modest antitumor activity in pretreated patients with advanced STS (response rate less than 20%) but yield disease stabilization. Some of these agents have shown the highest antitumor activity in selected histological subtypes such as taxane in angiosarcomas [81, 86], gemcitabine in leiomyosarcoma and angiosarcoma [87–89], dacarbazine in leiomyosarcoma and solitary fibrous tumor [5], and eribulin in liposarcoma and leiomyosarcoma [90]. Thus a personalized treatment based on a histology-driven approach may improve results and patients outcome.

Eribulin has been shown to improve OS by 2 months (13.5 versus 11.5 months) as compared with standard treatment dacarbazine in heavily pretreated patients with advanced liposarcomas or leimyosarcomas. A total of 452 patients have been enrolled in a randomized open label multicenter phase III trial (Study 309). The study's primary end point of OS was met. Eribulin reduced the risk of death by 23% (HR = 0.768; 95% CI 0.618–0.954; $P = 0.017$). However, secondary end points (PFS) were not significantly different (median PFS was 2.6 months in both arms). The 2 months improvement seen with eribulin must be weighed against the higher rates of adverse events in the eribulin group; neutropenia (44% versus 24%), peripheral sensory neuropathy (20% versus 4%), pyrexia (28% versus 14%), and alopecia (35% versus 3%), with higher rates of grade 3 (63% versus 53%), grade 4 (26% versus 20%), and toxic death (4% versus 1%) [91].

Trabectedin is a new agent that acts by binding to the minor groove of the DNA double strand and blocks the cell cycle in late S and G phases. Trabectedin results in a low response rate (8%) but yields prolonged disease stabilization. Leiomyosarcoma and myxoid liposarcoma appear to be more sensitive to trabectedin. A particularly higher activity was described in myxoid liposarcoma [92, 93]. It is approved for advanced previously treated STS in Europe on the basis a randomized phase II trial [93]. A recent phase III trial comparing trabectedin with dacarbazine in patients with liposarcoma and leiomyosarcoma confirms the results from the prior phase II study. The trial was conducted in 518 patients who previously received an anthracycline-containing regimen followed by at least one additional line of chemotherapy. The primary end point was OS. Secondary outcome measures included PFS, objective response rate, and safety. There was a highly statistically significant difference in PFS (4.2 months with trabectedin versus 1.5 months with dacarbazine HR = 0.55; $P < 0.0001$). However, this trial found no improvement in OS (median OS was 12.4 months with trabectedin versus 12.9 months with dacarbazine (HR = 0.87; 95% CI 0.644–1.181;

$P = 0.374$). The safety profiles were consistent with the well-characterized toxicities of both drugs [94].

Several other multi-agent combinations of active drugs in STS have been investigated. Doxorubicin plus dacarbazine leads to a response rate of 30% without a benefit in terms of OS [95, 96]. This regimen is a reasonable choice in the first-line treatment of leiomyosarcoma which is less sensitive to ifosfamide [5], or in patients in whom ifosfamide is contraindicated.

The combination of gemcitabine plus docetaxel is widely used in second-line treatment especially in leiomyosarcoma and undifferentiated pleomorphic sarcoma. The most relevant trial in this field has compared gemcitabine with and without docetaxel in patients with advanced STSs. This phase II randomized trial showed the combination to be superior to single-agent gemcitabine in terms of response rate, but also in terms of PFS and OS, but with increased toxicity [83].

The combination of gemcitabine and docetaxel shows no advantage over standard of care doxorubicin as first-line treatment of advanced STS. A recent prospective randomized controlled phase III trial compared this combination with single-agent doxorubicin as first-line treatment in advanced unresectable or metastatic STS. A total of 257 patients were enrolled. The primary end point was PFS rate (PFR) at 24 weeks. In the doxorubicin group 46.1% of patients were progression-free at 24 weeks versus 46% in the gemcitabine plus docetaxel group. The HR indicated superiority of doxorubicin (HR = 1.28; 95% CI 0.98–1.67; $P = 0.07$). Median OS was 71 weeks versus 63 weeks (HR = 1.07; 95% CI 0.77–1.49) for doxorubicin versus gemcitabine plus docetaxel, respectively. Thus, doxorubicin remains the standard first-line treatment for locally advanced/metastatic STS [97].

The combination of dacarbazine and gemcitabine was shown to improve the OS (16.8 versus 8.2 months) and PFS (4.2 versus 2 months) over dacarbazine in 113 patients with previously pretreated STS [98].

TARGETED THERAPIES

Pazopanib is an oral kinase inhibitor targeting VEGF-R, PDGFR, and c-KIT. It is the first and the only antiangiogenic drug approved for the treatment of refractory non-adipocytic soft tissue sarcoma [99]. After promising results in a phase II trial [100], a large randomized phase III trial (PALETTE) was conducted. The PALETTE trial showed a benefit in terms of PFS averaging 3 months (median 4.6 versus 1.6 months; $P < 0.0001$) for pazopanib given up to progression in refractory non-adipocytic soft tissue sarcoma patients [101]. However, no significant benefit in terms of OS was found; the median OS in patients treated with pazopanib was 12.5 versus 10.7 months in the placebo arm ($P = 0.25$). This was explained by the use of post-trial systemic therapy with other agents in the placebo group. The objective response rate was 6% for pazopanib versus 0% for placebo, with 67% stable diseases in the pazopanib arm versus 38% in the placebo arm [101]. In the PALETTE trial, adipogenic tumors were excluded on the basis of the lack of activity of pazopanib in this histology subtype in the phase II trial. However, an ongoing trial (ClinicalTrials identifier NCT1506596) will assess pazopanib's activity in adipocytic sarcomas including dedifferentiated, myxoid-round cell, pleomorphic, and mixed type [102], since these genetic subtypes have vascular patterns and may theoretically respond

to pazopanib [102]. The most common adverse events of pazopanib were fatigue, diarrheas, nausea, weight loss, and hypertension [101]. Retrospective analysis on pooled data from the previously cited phase II and III EORTC trials showed that good performance status, low/intermediate grade of the primary tumor, and a normal hemoglobin level at baseline were advantageous for long-term outcome. Long-term responders were defined as patients with PFS of at least 6 months (36%), long-term survivors as patients who survived for at least 18 months (34%) [103].

There is some evidence of the activity of several molecular targeted agents, including tyrosine kinase inhibitors and mammalian target of rapamycin (mTOR) inhibitors in selected histologies. However, these agents are not approved by regulatory authorities for the treatment of STS and should be preferably used within clinical trials [13].

Cediranib, a potent inhibitor of VEGFR receptors, has shown activity in alveolar soft part sarcoma (ASPS) with a disease control rate at 24 weeks of 84% in a phase II trial [104].

Sunitinib, an oral angiogenesis inhibitor, achieved promising results in patients with solitary fibrous tumors ($n = 10$) with 70% objective response and response duration of more than 6 months in five cases [105]. Sunitinib has also shown clinical efficacy in five of nine patients with ASPS treated with sunitinib 37.5 mg daily, continuously [106].

Crizotinib, an orally ATP-competitive inhibitor of the ALK and MET tyrosine kinases, has shown antitumor activity in ALK-rearranged inflammatory myofibroblastic tumor [107].

Regorafenib, a multikinase inhibitor, demonstrated promising activity and an acceptable toxicity profile in a recent randomized placebo-controlled phase II study (REGOSARC). The trial included 110 patients with metastatic STS. The patients were previously treated with doxorubicine, ifosfamide, trabectedin, or pazopanib (median of prior lines 2, range 1–3). The median PFS of leimyosarcoma patients was 4 months with regorafenib versus 1.9 months with the placebo (HR = 0.49; 95% CI 0.27–0.89; $P = 0.017$) and 4.6 months versus 1.0 month with regorafenib and placebo, respectively (HR = 0.38; 95% CI 0.20–0.74; $P = 0.002$) in other types of STS [108].

Ridaforolimus, an mTOR inhibitor, has been tested in a phase II trial conducted in 213 patients with advanced STS. Out of 193 patients with an evaluable response, 28% showed clinical benefit. These encouraging results led to a phase III trial (SUCCEED) which investigated maintenance therapy with ridaforolimus after chemotherapy in patients with metastatic STS. The PFS was improved with 52% gain in median PFS (22.4 weeks for ridaforolimus versus 14.7 weeks for placebo; HR = 0.72; $P < 0.001$). However, this trial failed to show a benefit in OS.

Sirolimus, another mTOR inhibitor, has resulted in significant clinical activity in patients with malignant perivascular epithelioid cell tumors (PEComa) through a mechanism involving the mTOR1 pathway, pathologically activated by loss of TSC1/TSC2 tumor suppressor complex in PEComa [109].

More recently, olaratumab, a human anti-platelet-derived growth factor alpha (PDGFα) monoclonal antibody has shown promising results in the treatment of advanced STS. It is the first agent added to doxorubine to achieve an improvement in OS (HR = 0.44; $P = 0.0005$) in a randomized phase II trial [110].

Despite a significant number of phase II trials of targeted therapies, a limited number of agents are tested in phase III trials.

Determining the optimal trial design and identifying the predictive biomarkers are crucial steps for the development of these drugs.

CONCLUSIONS

The management of adult STS is complex and should be carried out in a center with expertise in the treatment of sarcomas. A multidisciplinary approach is required for optimal outcome. Clinical guidelines still face some uncertainty given the heterogeneity of the available data. New methods for clinical trials are needed to generate reliable evidence for standard practice.

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