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Advances in the Management of Soft Tissue Sarcomas - Focus on Emerging Therapies

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Abstract

Soft Tissue Sarcoma (STS) encompasses a number of different clinical entities and is a rare form of cancer. This review focuses on treatment of extremity and trunk STS (excluding gastrointestinal stromal tumors), focusing on more recent treatment updates. Early disease is managed by surgical resection as a definitive curative procedure, sometimes in combination with radiotherapy. Newer techniques have decreased the burden of resection and allowed safer delivery of radiation. Adjuvant chemotherapy cannot be recommended as a general approach but is used in individual cases with high-risk, chemosensitive tumours. Advanced disease poses even more dilemmas in terms of management, and outcomes are generally poor. Research in systemic treatment has not had major breakthroughs in field of STS in the last 30 years. Doxorubicin is the standard first line treatment, while ifosfamide and dacarbazine are the most often used second line therapy. Eribulin and Trabectedin have been approved as second line therapies in more recent times. Targeted therapy is of particular interest and newer agents are becoming available for use. Pazopanib is used in non-adipocytic sarcoma after progression on chemotherapy. A number of newer agents are harbouring interest including olarutamab, cediranib and aldoxorubicin. The major focus in oncology research is currently in the field of immunotherapy, and more mature data in STS is awaited. Ultimately management is best performed in a specialist unit with a multi-disciplinary approach to improve patient outcomes. Clinical trial participation remains the preferred approach for patients with advanced disease.

Introduction

STS encompasses a number of different subtypes with up to 50 different forms based upon the related cell type [1]. These tumours originate from pluripotent cells of the mesenchyme and are extremely rare making up less than 1% of overall cancer diagnoses [1,2]. Surgical resection with adequate margins remains the key to treatment of localised disease, however advanced disease requires a multimodal approach [3]. Chemotherapy regimens over time have become more suited to treatment of the disease particularly with the addition of targeted therapy. Such newer agents are aimed at the different subsets of soft tissue sarcoma and have shown promising results in certain groups [1]. Radiotherapy as an adjunct to surgery is commonly used particularly in tumours of the extremity, but adjuvant chemotherapy has not been shown to increase survival [4]. This paper will aim to explore current treatment options, with particular attention to the emerging therapies now available.

Presentation and Work-up

STS can present in a multitude of different ways, depending upon location and size. The usual presenting symptom, is a mass, generally not painful, which has increased in size over time. If the tumour grows into surrounding structures, then this may cause symptoms including altered sensation, lymphatic obstruction or bowel and/or urinary symptoms [1,5]. Once patients have been seen by a specialist, the next step in further assessment will be imaging to define the mass. Computed Tomography (CT) will provide information related to likely source and relation to other structures (Figure 1). To stage the patient the chest, abdomen and pelvis should be imaged with CT as well [1,5]. CT angiogram could be useful, if there are adjacent vascular structures at risk, particularly if resection is planned. Magnetic Resonance Imaging (MRI) can assist in differentiating the tissue of origin and has been found to be particularly useful when assessing soft tissue sarcoma of the extremities. PET CT is not always a part of the routine work-up, though it can show malignant spread or provide other differentials for the mass [1,5]. Imaging techniques will usually

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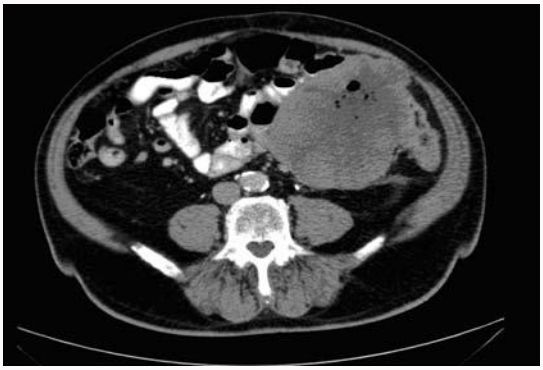

Figure 1: Axial CT image – showing large retroperitoneal sarcoma invading into small bowel mesentery.

give sufficient information, but if management will be affected then biopsy can be done to confirm diagnosis. In tumours of the periphery this can usually be done by core biopsy of the tumour, which will generally give an adequate sample. Fine Needle Aspirate (FNA) will often not provide sufficient tissue for tumour assessment and is not recommended. The tract for biopsy should be made in a way that it can be excised once definitive resection is planned. In soft tissue sarcoma of the retroperitoneum, biopsy should be undertaken with care, due to risk of tumour seeding to surrounding structures [1,5]. A recent retrospective analysis however showed no significant risk of tumour seeding if retroperitoneal sarcomas were biopsied [6].

Distribution and Staging

Given the origin of soft tissue sarcoma, many regions and tissue types can be affected by tumour. Most lesions affected either the upper or lower limb, which can account for up to 60% of tumours. The retroperitoneum or peritoneal space are the next most common location for these cancers. Head and neck lesions, plus those of the trunk are less common than the above, but are still seen in up to 10% of presentations [1,5].

As previously mentioned over 50 subtypes exist, though some are encountered more frequently. Liposarcoma and Leiomyosarcoma are the most common types of soft tissue sarcoma. Accounting for approximately 20% of tumours respectively. Fibro sarcomas and synovial sarcomas are the next most common lesions that are encountered in clinical practice. Gastro-intestinal stromal tumour was once considered a form of Leiomyosarcoma, but they are now considered separately to soft tissue sarcomas entirely [5].

Staging of soft tissue sarcoma gives prognostic information and is adapted from the IUCC -AJCC TNM system (International union against cancer; American joint committee on cancer). Tumour grade is divided into 4 categories (I-IV) and further separated into low (I,II) and high grade (III,IV). This is assessed on histological review of features such as mitotic grade, necrosis, presence of de-differentiation, cellular changes and content of stroma. Low grade lesions have a significantly lower rate of distant metastasis (<15%) compared to high grade tumours (>50%). TNM classification of sarcoma assesses the size of lesions and depth of invasion for T staging, presence of nodal disease or distant metastasis completes staging [1,5] (Table 1 and 2).

Surgery

Given the distribution of STS, surgical resection with clear margins remains challenging even in the hands of the most experienced surgeon. Tumours of the retroperitoneum constitute 15% of all soft tissue sarcoma. Wide local excision is difficult due to the need to preserve vital structures in the vicinity [4]. In the management of low-grade tumours, resection with wide margins is the standard of care. A recent Australian study showed close margins of >1mm did not affect outcomes, though this is not widely accepted [3]. Wider margins of at least 2-3cm have been shown in numerous papers to reduce rates of local recurrence. It is therefore suggested that specialist surgical teams be involved in resection with general surgical and orthopaedic sarcoma experts [3,4]. Soft tissue sarcoma disseminates via haemotogenous spread, therefore extensive lymph node dissection is not required [5].

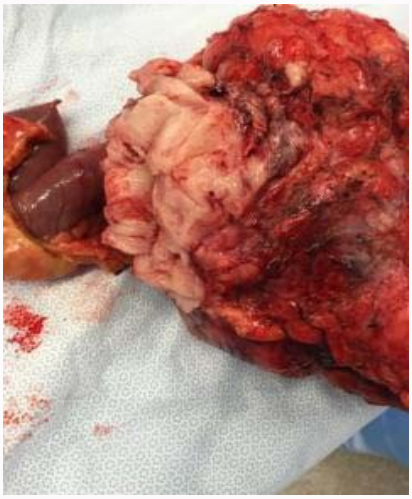

Figure 2: Operative Specimen showing large poorly differentiated sarcoma, resected en bloc with surrounding small and large bowel.

STS form pseudo capsule from the tissue of origin, which has been compressed by growth. Malignant cells can spread beyond this, meaning a macroscopically clear margin does not always mean complete excision [4]. Wide local excision does not simply involve the removal of the visible tumour but includes surrounding tissue to reduce recurrence [3], (Figure 2) Patient outcomes have been shown to be improved when sarcoma is managed in specialised units with a multidisciplinary approach [7].

Dickinson et al. [3], suggested that in low-grade sarcomas their specialist unit did not routinely use adjuvant chemoradiotherapy and this did not affect outcomes. It was also suggested that to avoid morbidity in these patients undertaking radical resection, that vital structures do not need to be resected just to obtain wide margins [3]. The risk of local recurrence *vs.* overall quality of life need to be weighed up in deciding what is best for the patient. Clark et al. [4] suggested when resection is combined with radiotherapy in sarcoma of the extremity, a recurrence rate as low as 4% is possible, if margins are left positive to allow the limb to be preserved. In management

Table 1: Sarcoma grading.

Grade	Description
Grade 1	Well differentiated
Grade 2	Moderately differentiated
Grade 3	Poorly differentiated
Grade 4	Undifferentiated

of tumours of the head and neck there are many challenges related to obtaining clear margins and acceptable cosmesis [8]. MOHS micrographic surgery has been used in this setting. This involves taking small segments of tissue at the resection margins, sending them for frozen section and having them reviewed by a histopathologist intraoperatively [8]. The aim is to confirm clear microscopic margins in real time and to limit the amount of normal tissue taken with the tumour. Loghdey et al. [8] showed a significant reduction in local recurrence in patients who underwent MOHS surgery for Dermatofibrosarcoma Protuberans (1.1%) versus traditional wide local excision (7.3%). Plastic and reconstructive surgeons are best involved in tumours of the head and neck to utilise such techniques [9]. Tissue expanders can be used to fill such defects from the tumour resection and to improve aesthetics [10].

Radiotherapy

Radiotherapy can be used in limb-sparing surgery to reduce local recurrence rates. It is most often an adjunct to surgical resection in high grade sarcoma [3]. This can be given as neoadjuvant or more commonly adjuvant treatment and is particularly useful if margins are suspected to be close or involved [4]. Mann et al. [11] suggested however that morbidity is worse when radiotherapy is given pre-operatively and there are increased rates of secondary procedures [5]. Site of the tumour certainly affects its safe use, particularly in relation to retroperitoneal sarcoma, where safe delivery of radiation is problematic [3]. When circumstances do not permit surgical excision of tumour, radiotherapy has been used as a primary treatment for sarcoma. Higher fraction external beam radiation is required to be effective though in this setting, and management is aimed to prevent further local spread of disease [5]. Delivery methods include external beam radiation and brachytherapy, dependent upon site and accessibility of the tumour. There is limited evidence to suggest which provides better results, therefore specialist decision will guide the choice of delivery method [3]. Low grade tumours often will not require radiotherapy treatment if clear margins have been obtained.[4] Though some studies have examined its use in such settings, evidence remains in favour of its use with high grade or large tumours [5]. Retroperitoneal soft tissue sarcomas pose resection dilemmas as well as challenges in the delivery of radiotherapy. Major vessels of the alimentary tract, bowel and solid organs are at risk of collateral damage and should be spared where possible [3]. To assist with the administration of radiotherapy a novel technique of leaving a tissue expander within the tumour bed after resection has been proposed. This allows the field for external beam radiation to remain clear of structures such as bowel, increasing the overall fraction that can be delivered safely [9]. High local recurrence rates in retroperitoneal sarcomas lead to the development of this technique. Data to prove this techniques overall efficacy is not particularly strong, though it has been shown to be safe. A recent observational study suggested higher dose radiation was able to be given in patients who had tissue expanders inserted and also suggests a significant reduction in local disease recurrence rates [10]. From this it can be said that radiotherapy is best utilised in the adjuvant setting particularly in tumours of the extremity. Low grade lesions should not need radiotherapy, when wider excision is possible, except in larger lesions greater than 5cm [5]. Lindberg et al. [11], though showed that in limb preservation surgery adjuvant radiotherapy provided recurrence rates as low as 6% in low grade lesions, that had radiotherapy post-operatively. Poorly differentiated tumours as expected have higher recurrence rates, though adjuvant radiotherapy has been suggested to be effective in such lesions [4,11].

Table 2: Sarcoma staging.

TNM Staging	Description
T1	Tumour <5cm in largest dimesion
T1a	Superficial tumour
T1b	Deep tumour
T2	Tumour >5cm in largest dimension
T2a	Superficial tumour
T2b	Deep tumour
N0	No nodal disease
N1	Regional Lymph nodes
M0	No distant metastasis
M1	Distant metastasis

Staging				
Stage Ia	G1/G2	T1a/b	N0	M0
Stage Ib	G2	T2a/b	N0	M0
Stage IIa	G3/4	T1a/b	N0	M0
Stage IIb	G3/4	T2a	N0	M0
Stage III	G3/4	T2B	N0	M0
Stage IV	Any G	Any T	N1	M1

Adapted from Mann et al. [15]

Table 3: Predicted chemosensitivity of soft tissue sarcoma subtypes.

Chemosensitive	Desmoplastic small round cell tumour
	Synovial sarcoma
	Myxoid/round cell liposarcoma
	Uterine leiomyosarcoma
Moderately chemosensitive	Pleiomorphic liposarcoma
	Epithelioid sarcoma
	Leiomyosarcoma
	Angiosarcoma
Relatively chemo-insensitive	Malignant peripheral nerve sheath tumour
	Myxofibrosarcoma
	Dedifferentiated liposarcoma
	Clear cell sarcoma
	Endometrial stromal sarcoma
Chemoinsensitive	Alveolar soft part sarcoma

Adapted from A. Dangoor et al. [18]

Systemic Treatment

Adjuvant treatment: Adjuvant chemotherapy in soft tissue sarcoma remains a controversial topic. Early trials utilizing doxorubicin have suggested benefit in using adjuvant chemotherapy but none of the trials showed statistically significant difference in overall survival. Meta-analysis of these early trials, conducted by SMAC and published in Lancet in 1997 showed statistically significant difference in relapse free survival and recurrence rates, but no statistically significant difference in overall survival [2]. Ifosfamide, although known to be effective agent in STS, was not used in the early adjuvant trials because of dose limiting toxicity, leading to acute haemorrhagic cystitis. In the 80's, after Mesna was shown to be effective in preventing haemorrhagic cystitis, subsequent trials incorporated ifosfamide. The updated analysis that

Table 4: Combination Chemotherapy Regimens.

Regimen	Phase	Trial	Response rate (%)	PFS (months)	OS (months)
Doxorubicin + Ifosfamide + Dacarbazine (MAID)	II	Antman et al. [46] Elias et al. [47]	32-49	06-10	13-16
Doxorubicin + Ifosfamide	III	Judson et al. [19]	26	7.4	14.3
Doxorubicin + Dacarbazine	II	Borden et al. [20]	30	3.6	8
Gemcitabine + Docetaxel	II	Maki et al. [29]	16	6.2	17.9
Gemcitabine + Dacarbazine	II	Garcia-del-Muro et al. [48]	12	4.2	16.8

Table 5: Single Agent Chemotherapy.

Agent	Phase	Trial	Treatment line	Response rate (%)	PFS (months)	OS (months)
Doxorubicin	II	Borden et al. [20]	Any line	19	3	8
	III	Judson et al. [19]	1st	14	4.6	12.8
Dacarbazine	II	Buesa et al. [26]	≤3 prior lines	18	2	
Ifosfamide	II	Van Oosterom et al. [49]	1st 2nd	10-25 6-8		10-12 (1st line) 8-10 (2nd line)
Pegylated liposomal doxorubicin	II	Judson et al. [21]	1st	10	3	11
Eribulin	III	Schoffski et al. [34]	2nd	4	2.6	13.5
Trabectedin	III	Demetri et al. [35]	2nd or 3rd	9.9	4.2	12.4

Table 6: Targeted Therapy.

Agent	Sarcoma Subtype	Phase	Trial	Response rate (%)	PFS (months)	OS (months)
Imatinib	DFSP	II	Rutkowski et al. [38]	45.9	Not reported	Not reported
Pazopanib	Multiple	III	Van der Graaf et al. [39]	6	4.6	12.5
Cediranib	ASP	II	Kummar et al. [40]	35	Not reported	Not reported
Olaratumab + doxorubicin	Multiple	II	Tap et al. [42]	18.2	6.6	26.5

included newer generation trials with ifosfamide showed survival benefit for combination protocols that included ifosfamide [12]. However, two large EORTC trials, both using doxorubicin and ifosfamide based protocols did not show difference in survival with adjuvant chemotherapy [13-15]. Based on these results, adjuvant chemotherapy is not recommended as standard approach, but it can be considered on the individual basis, depending of the risk features and chemosensitivity of tumor.

Advanced disease: Metastatic soft tissue sarcoma is a terminal diagnosis for most of the patients apart for the select few that are amenable to metastasectomy. The treatment intent and choice of treatment modality is complex and requires multidisciplinary involvement that includes medical and radiation oncology as well as palliative care and ssurgical teams. Reported median survival for advanced STS is in the range of 12-18 months, although it varies significantly, depending on the subtype of tumour, disease burden and performance status [16]. A recently published Australian multicenter study reported that one-third of patients with advanced disease received systemic treatment, and a similar percentage of patients underwent radiotherapy or metastasectomy for palliation [17]. The choice of treatment modalities will depend on the site and extent of disease, presence of symptoms and performance status, and predicted chemosensitivity and Radiosensitivity of the tumour. Chemosensitivity varies depending on the subtype. Liposarcoma and synovial sarcoma are considered more chemosensitive whereas undifferentiated pleomorphic sarcoma does not respond well to chemotherapy [16,18], (Table 3).

Chemotherapy

For the patients deemed fit for systemic treatment, standard of care is cytotoxic chemotherapy for the majority of tumour subtypes. Doxorubicin is the first line treatment of choice in advanced soft tissue sarcoma [1]. It was one of the first agents to show activity in sarcoma and the the response rates average in the range of 15-20%, depending on the study [19,20]. Increased response rates have been achieved with adding another cytotoxic agent (ifosfamide, [19], dacarbazine [20]) to doxorubicin. No trial has shown improved survival advantage and toxicity is increased with combination treatment. Based on these results, combination chemotherapy remains a reasonable choice in fit patients with significant burden of symptoms, where tumour shrinkage will likely result in improved quality of life; but can not be recommended as general principle.

Other anthracyclines that were investigated for STS include pegylated liposomal doxorubicin (PLD), and aldoxorubicin. A phase II randomized study that compared PLD with standard doxorubicin found a similar response rate between groups (10 and 9 percent resepectively). There was also a different adverse event profile – haematological toxicity was higher with doxorubicin, while skin toxicity was more common in PLD arm [21]. Aldoxorubicin is a new form of albumin-bound doxorubicin, which is designed with the idea that albumin carries doxorubicin to the more acidic tumour environment, where the bond is then disconnected. This way, the drug accumulates in tumour environment, allowing higher concentrations of doxorubicin with less systemic toxicity [22]. In a phase IIb randomized multicenter study, aldoxorubicin was compared to doxorubicin and the results showed improved progression-free survival in the experimental arm (5.6 [95% CI, 3.0-8.1] *vs.* 2.7 [95% CI, 1.6-4.3] months; P = .02). Response rates were higher in the aldoxorubicin group as well (20 percent *vs.* 0 percent), but grade 3 or 4 neutropenia was also more common (29 *vs.* 12

percent), but not febrile neutropenia [23]. Ifosfamide, a nitrogen mustard alkylating agent, has response rates of up to 18% as a single agent therapy [1,24]. It can be used as an alternative to anthracyclines in cases with contraindications i.e. cardiac failure or intolerance. It has a more established role as a second line agent, after progression on anthracyclines. Tumours that develop resistance to standard-dose ifosfamide can be respond to increased dose but at the cost of increased toxicity [25]. Dacarbazine (DTIC) along with doxorubicin is one of the oldest drugs to have shown activity in STS. It was first described as a possible option as a monotherapy in advanced disease, with reported response rate of 18%; but a relatively short time to progression [26]. Subsequent trials investigated its use in combination with Doxorubicin. Borden et al. [20] showed increase in response rates compared to Doxorubicin alone, in patients with metastatic disease. With the emergence of Mesna, which enabled administration of high-dose Ifosfamide as an option for dual therapy, Dacarbazine has fallen out of favor, and has become reserved for patients who did not tolerate the side effects of this newer agent. A systematic review published in 2013 by Sharma et al. [27] investigated its use as second line therapy with and without Gemcitabine. They showed a 54.2% rate of disease free progression at 3 months when used as combination therapy, compared to 35.2% in the single treatment groups. Gemcitabine is another active agent with a reported response rate of 18% [28]. Combination of gemcitabine with docetaxel has shown to increase response rates, even though docetaxel on its own does not have significant activity in STS. A randomised phase II study by Maki et al. [29] showed tumour response rates of 8% with gemcitabine alone compared to 16% with combination therapy of gemcitabine and docetaxel. Docetaxel as a first line therapy or as a single second line agent has also been examined in advanced disease with limited success [30]. In phase III GeDDiS trial, gemcitabine / docetaxel combination was compared with doxorubicin in the first-line. The primary end-point, progression-free survival was similar in both arms (HR 1.28, 95% CI, 0.98–1.67; P = .07) but the combination arm had more dose delays and patient withdrawals due to toxicity [31]. The results reaffirmed the role of doxorubicin as preferred first-line choice in STS. Taxanes in general have not shown action across most subtypes of STS, hower angiosarcoma seem to be particularly sensitive to taxanes. Response rates of up to 64 percent have been reported in a retrospective study published by EORTC soft tissue and bone sarcoma group [32]. Their activity was confirmed in prospective phase II ANGIOTAX study, although the response was more modest (18.5%) [33]. This makes paclitaxel an agent of choice in first-line treatment of this sarcoma subtype. Newer agents are harbouring interest including Eribulin, a medication derived from marine sponges, that acts to inhibit mitosis by blocking production of cellular microtubules [1]. A phase III trial by Schoffski et al published earlier this year, compared Eribulin to Dacarbazine in second line treatment of advanced Liposarcoma and Leiomyosarcoma. They found a significant overall survival benefit: 13.5 months Eribulin group compared to 11.5 months in the dacarbazine group. Interestingly, the survival increase was seen but there was no significant difference in progression-free survival [34]. Patient with Liposarcoma had the most significant benefit from treatment, so it has been approved by the FDA for treatment in this type of sarcoma.

Trabectedin is another active agent that is now used in the treatment of metastatic and locally advanced Liposarcoma but also in Leiomyosarcoma [1]. It too was originally derived from marine aquatica, but from sea tunicates. In a randomized phase III study this agent was compared to Dacarbazine in patients with pretreated liposarcoma or Leiomyosarcoma; and found it significantly improved progression free survival (4.2 months *vs.* 1.5 months - HR 0.55; p <0.001). The overall survival difference though was not statistically significant [35]. Both treatments were well tolerated, with similar rate of myelosupression but higher frequency of transient elevation of transaminases in trabectedin arm.

Targeted Therapy

With the success of the tyrosine kinase inhibitor imatinib in treatment of gastrointestinal stromal tumours [36] the attention has shifted to small molecule targeted agents as a potential solution to overcoming resistance of STS to cytotoxic chemotherapy. However, subsequent studies with imatinib did not show equally impressive results in other histological subtypes [37] except for dermatofibrosarcoma protuberans that harbor translocation 17:22, where partial response was reported in 46% of patients [38]. Pazopanib, a potent multitargeted tyrosine-kinase inhibitor was the first treatment that had phase III date published in second line setting for STS. The study excluded adipocytic sarcoma based on negative signal for this subtype in phase II trial, and patients were randomized to pazopanib or placebo, with no subsequent cross-over. The primary end point of progression-free survival was significantly improved in experimental arm (4.6 *vs.* 1.6 months), but the overall survival difference was not significant (12.5 *vs.* 10.7 months) [39]. Positive results with pazopanib have ignited interest in using other VEGF inhibitors, with several positive phase II trials reported to date. Cediranib has shown 35% response rate in single arm study of patients with alveolar soft part sarcoma – a highly vascular subtype of sarcoma [40]. Sunitinib was trialed in heterogeneous group of sarcomas, with one partial response out of 48 patients, and disease control rate of 23% at 16 weeks [41]. Olaratumab, a monoclonal antibody which inhibits human Platelet-derived growth factor receptor alpha (PDFGRa), has shown exciting progress in advanced disease. A study published recently published in the Lancet by Tap et al. [39], compared the activity of Doxorubicin in metastatic and locally advanced soft tissue sarcoma to Doxorubicin and Olaratumab. In the phase II part of the trial, participants were randomized to receive doxorubicin 75 mg/m^2 with olaratumab or placebo. The primary end point was progression free survival which was2.5 months longer in experimental arm, but a much more significant difference was noted in overall survival. An 11.8 month difference in the dual therapy group compared to standard chemotherapy regimen [42]. A phase III confirmatory trial has completed recruitment.

Immunotherapy

Immunotherapy has been the latest breakthrough in oncology treatment with remarkable results achieved in treatment of metastatic melanoma with Checkpoint Inhibitors (CPI). CPI are monoclonal antibodies that bind to surface receptors of immune cells and/or tumor cells and modify immune response of the host to the tumour. Response rates in melanoma in phase III studies were up to 40 percent with PD-1 inhibitors [43] and up to 58 percent with combination CTLA-4 and PD-1 inhibitors [44], and a proportion of the patients achieve ongoing long term disease control. In some subtypes of STS, responses have been reported but overall response rates are disappointing compared to some tumour subtypes. A multicenter phase II study of PD-1 inhibitor pembrolizumab in STS and bone sarcomas presented at 2016 American Society of Clinical Oncology Annual Meeting reported no responses in 29 patients

with leiomyosarcoma, liposarcoma and synovial sarcoma, but there were 2/9 patients with undifferentiated pleomorphic sarcoma that had a response [45-49]. However, further studies are ongoing, and numerous new checkpoint inhibitors are currently being tested alone or in combination.

Conclusion

From the above review it can be said that sarcoma diagnosis remains a complex clinical problem, in terms of management as well as addressing research design. Given the heterogeneity of disease presentation and low incidence, the management of potentially curable disease requires involvement of multidisciplinary team, experienced in treating these tumors in high-volume centers. Advanced sarcoma continues to have poor prognosis, with only a minority of patients achieving meaningful benefit from cytotoxic chemotherapy. Encouraging results with targeted agents are offering promise in certain subtypes of sarcoma but more mature data and confirmation studies are awaited. A number of early trials involving targeted and immunotherapy agents are ongoing, and patient enrolment is strongly encouraged in this area of desperate need for effective treatments.

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