Clinics in Oncology

Review Article
Published: 08 Mar, 2018

Metastatic Soft Tissue Sarcomas: A Review of Treatments and New Pharmacotherapies

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Abstract

Soft Tissue Sarcomas (STS) are a heterogeneous group of rare tumors which arise from mesenchymal cells. The malignant precursor cells may differentiate into several lineages such as muscle, adipose, fibrous, cartilage, nerve or vascular tissue to name a few. There are over 50 different subtypes of soft tissue sarcomas, of which undifferentiated pleomorphic sarcoma, adipocytic sarcoma, leiomyosarcoma, nerve sheath sarcoma being more common. The treatment options for soft tissue sarcoma include surgery, radiation therapy, chemotherapy and targeted therapy. In this article we focus on approved treatments and newer therapeutic approaches for management of soft tissue sarcomas.

Introduction

Soft Tissue Sarcomas (STS) are mesenchymal neoplasms with over 50 subtypes (Figure 1), which vary in molecular, histological and clinical characteristics. They can occur in any site within the body, with extremity, trunk, head and neck, and retroperitoneum being the most common sites. The most common subtypes are Undifferentiated Pleomorphic Sarcoma (UPS), Liposarcoma (LPS), Leiomyosarcoma (LMS), Synovial Sarcoma(SS), and Malignant Peripheral Nerve Sheath Tumors (MPNSTs). Incidence of STSs is rare, with occurrence rate of <1% of adult cancers [1]. Metastasis is common, with up to 50% high grade STSs developing metastases and often die of their disease [2]. TNM staging of soft tissue sarcoma is shown in Table 1. STS is one of the 5 most common causes of cancer related death in young adults and pediatric patient population [1]. Historically, the median Overall Survival (OS) for advanced metastatic STS is about 12 months, whereas the more recent studies with newer drugs have shown overall survival improving up to 18 months. Thus, improvements in treatment modalities are further required [3]. In this article we review treatment options for some of the common and uncommon subtypes of soft tissue sarcomas.

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Received Date: *15 Jan 2018*
Accepted Date: *20 Feb 2018*
Published Date: *08 Mar 2018*

Citation:
Seetharam M, Kolla KR, Chawla SP. Metastatic Soft Tissue Sarcomas: A Review of Treatments and New Pharmacotherapies. Clin Oncol. 2018; 3: 1426.

General Treatment Approach of Metastatic Soft Tissue Sarcoma

The most common route of spread of soft tissue sarcomas is hematogenous, mostly to lungs [4]. Lymph node metastasis is uncommon except with epithelioid sarcomas, rhabdomyosarcomas, angiosarcomas and clear cell sarcomas [5]. Treatment of metastatic STS is challenging, and the treatment is mostly palliative with median OS of 12 months to 18 months. Chemotherapy is the standard approach, and sometimes combined with surgical resection (metastatectomy), with reported survival benefit [6].

Systemic management

First line chemotherapeutic agents:

a. Doxorubicin +/- Ifosfamide: A randomized phase III trial in 326 patients with advanced soft tissue sarcoma compared Doxorubicin (doxo) versus with two different treatment schedules of ifosfamide (continuous IV infusion vs. bolus ifosfamide). Results showed no difference between the three arms. The progression free survival was 2.52 months (doxo group) versus 2.16 months (ifosfamide group) and overall survival of 12 months (in doxo group) versus 10.92 months (ifosfamide group) (p =0.076) [7].

The phase III EORTC 62012 trial compared doxorubicin versus doxorubicin with ifosfamide. The results showed higher response rate and progression free survival with the combination but no statistically significant improvement in overall survival (PFS: 7.4 months (doxo + ifosfamide) and 4.6 months (doxo alone group) p =0.003); overall survival: 14.3 months (doxo + ifosfamide) versus 12.8 months (doxo alone) p =0.076). The one year overall survival was numerically higher with combination but not significant. The combination therapy had higher grade 4 toxicities. Thus, based

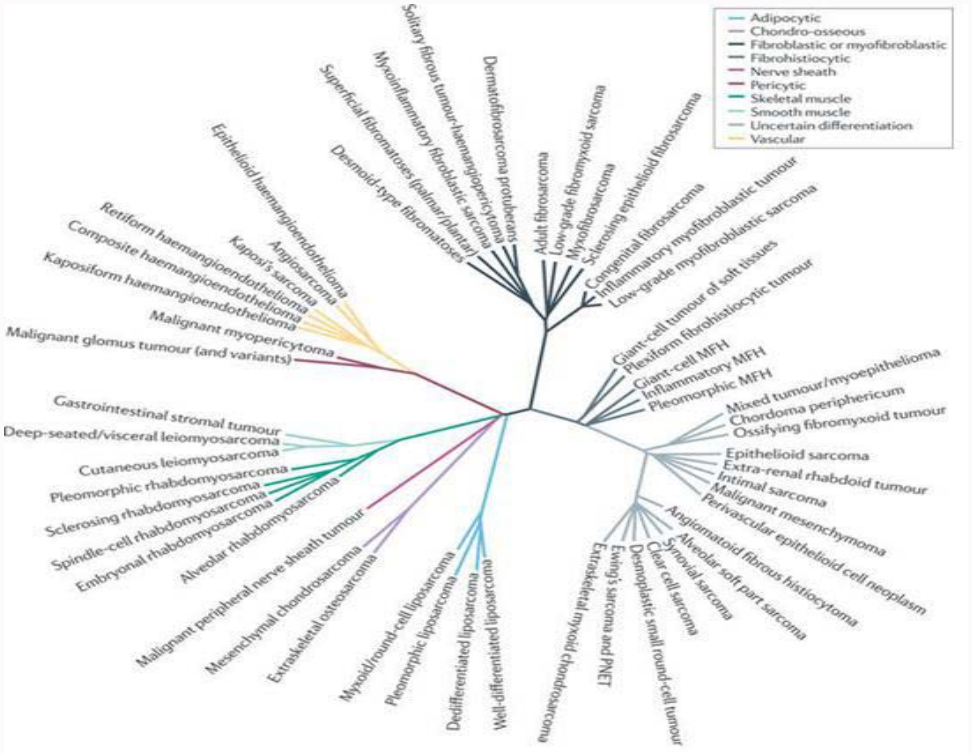

Figure 1: Sarcoma subtypes.

on the results, the combination of DOX-IFO still remains a standard treatment option in patients who are in need for a response prior to potential surgical resection or with symptomatic metastatic disease [8].

b. Doxorubicin +/- Olaratumab: Based on phase II data, olaratumab obtained conditional approval from FDA and EMA in combination with doxorubicin for patients with metastatic soft tissue sarcoma in late 2016. The phase II study compared the combination against doxorubicin single agent as first line treatment for metastatic soft tissue sarcoma. The median OS (Overall Survival) was 26.5 months with combination versus 14.7 months with doxorubicin alone (HR 0.46, p =0.0003). The PFS was 6.6 months with combination versus 4.1 months with doxorubicin alone (HR 0.67, p =0.0615). Although confirmatory phase III data is pending, olaratumab is still considered an optional agent, but nevertheless promising [9].

c. Gemcitabine +/- Docetaxel: In randomized phase II trials, Docetaxel in combination with gemcitabine has demonstrated activity, especially in uterine leiomyosarcoma compared to gemcitabine alone. The response rate was 16 vs. 8%, with median PFS 6.2 months vs. 3 months and median OS of 17.9 months vs. 11.5 months in Docetaxel + gemcitabine versus gemcitabine groups respectively [10].

d. Doxorubicin vs. Docetaxel/Gemcitabine: In the randomized phase III trial, doxorubicin was studied against combination of gemcitabine and docetaxel in first line treatment of advanced unresectable or metastatic soft tissue sarcoma. The results showed no significant difference in proportion of patients alive and progression free at 24 weeks between both the groups [46.3% (95% CI 37.5 - 54.6) vs. 46.4% (37.5 - 54.8)]; median progression free survival was 23.3 weeks in doxorubicin group (95% CI 19.6 - 30.4) vs. 23.7 weeks in gemcitabine and docetaxel group (95% CI 18.1 - 20.0) (hazard ratio for PFS was 1.28, 95% CI 0.99 - 1.65, p =0.06) [11].

Second line and beyond systemic therapies:

a. Trabectedin: Trabectedin, an alkylating agent derived from Caribbean Sea squirt was approved by the FDA in 2015 for metastatic liposarcoma and leiomyosarcoma (L-sarcomas). The phase III trial of trabectedin versus dacarbazine showed median progression free survival of 4.2 months with trabectedin, and 1.5 months with dacarbazine, Clinical Benefit Rate (CBR) was 34% (trabectedin group) versus 19% (dacarbazine). The median overall survival was 12.4 months (trabectedin group) versus 12.9 months (dacarbazine group) (HR 0.87, p =0.37) [12].

b. Pazopanib: Based on results from phase III (PALETTE) trial, pazopanib, an oral tyrosine kinase inhibitor was approved for non-adipocytic sarcomas. The study compared pazopanib vs. placebo in patients who had progressed on anthracycline based regimen. The results showed a median PFS of 4.2 versus 1.5 months, and disease stabilization of 67 versus 38% favoring pazopanib in patients with non-adipocytic sarcomas progressing after first line chemotherapy. Overall survival was 12.5 months (pazopanib group) versus 10.7 months (placebo group) (p =0.25) [13].

c. Dacarbazine +/- Gemcitabine: In a randomized phase II trial, combination of Gemcitabine and Dacarbazine every 14 days versus dacarbazine alone showed improved median PFS (4.2 months versus 2 months) and overall survival (16.8 months versus 8.2 months), especially in leiomyosarcoma [14].

d. Gemcitabine +/- Docetaxel: In randomized phase II trials, docetaxel in combination with gemcitabine showed activity in uterine leiomyosarcoma compared to gemcitabine alone. The RR was 16 vs. 8% favoring the combination, with median PFS of 6.2 months vs. 3 months and OS of 17.9 months vs.11.5 months favoring docetaxel + gemcitabine [10].

Table 1:

TNM staging for soft tissue sarcoma				
Primary tumor (T)				
TX	Primary tumor cannot be assessed			
T0	No evidence of primary tumor			
T1	Tumor 5 cm or less in greatest dimension*			
T1a	Superficial tumor			
T1b	Deep tumor			
T2	Tumor more than 5 cm in greatest dimension*			
T2a	Superficial tumor			
T2b	Deep tumor			
Regional lymph nodes (N)				
NX	Regional lymph nodes cannot be assessed			
N0	No regional lymph node metastasis			
N1¶	Regional lymph node metastasis			
Distant metastasis (M)				
M0	No distant metastasis			
M1	Distant metastasis			
Histologic grade (G)Δ				
GX	Grade cannot be assessed			
G1	Grade 1			
G2	Grade 2			
G3	Grade 3			
Anatomic stage/prognostic groups				
Stage IA	T1a	N0	M0	G1, GX
	T1b	N0	M0	G1, GX
Stage IB	T2a	N0	M0	G1, GX
	T2b	N0	M0	G1, GX
Stage IIA	T1a	N0	M0	G2, G3
	T1b	N0	M0	G2, G3
Stage IIB	T2a	N0	M0	G2
	T2b	N0	M0	G2
Stage III	T2a, T2b	N0	M0	G3
	Any T	N1	M0	Any G
Stage IV	Any T	Any N	M1	Any G

Note: cTNM is the clinical classification, pTNM is the pathologic classification.
*Superficial tumor is located exclusively above the superficial fascia without invasion of the fascia; deep tumor is located either exclusively beneath the superficial fascia, superficial to the fascia with invasion of or through the fascia, or both superficial yet beneath the fascia.
¶Presence of positive nodes (N1) in M0 tumors is considered Stage III.

e. Doxorubucin vs. Gemcitabine/Docetaxel: In the randomized phase III trial, frontline doxorubicin versus gemcitabine and docetaxel was compared in patients with advanced unresectable or metastatic soft tissue sarcoma. Results showed no significant difference in proportion of patients alive and progression free at 24 weeks between both the groups (46.3% (95% CI 37.5 - 54.6) vs. 46.4% (37.5 - 54.8)); median progression free survival was 23.3 weeks (doxorubicin group) (95% CI 19.6 - 30.4) vs. 23.7 weeks (gemcitabine and docetaxel) (18.1 - 20.0) (hazard ratio for PFS was 1.28, 95% CI 0.99 - 1.65, p =0.06) [11].

f. Aldoxorubicin vs. Doxorubicin: A phase 2b, open randomized study was conducted to evaluate efficacy and safety of Aldoxorubicin (ALDOX) compared to doxorubicin in patients with advanced soft tissue sarcomas. Results showed that single agent aldoxorubicin therapy demonstrated improvement in progression free survival (5.6 months in ALDOX group Vs 2.7 months in doxorubicin group) and six months progression free survival (46% and 23% in ALDOX and doxorubicin groups respectively). ALDOX therapy exhibited manageable adverse effects and no evidence of acute cardiotoxicity [15].

g. Aldoxorubicin vs. Investigators' choice treatment: A phase III open-label study was conducted to compare safety of Aldoxorubicin (A) to Investigators Choice (IC) of treatment (dacarbazine, doxorubicin, pazopanib, ifosfamide, and gemcitabine/docetaxel) in Soft Tissue Sarcoma (STS) patients, who have relapsed or were refractory to prior chemotherapy. Results (summarized in Table 2), found that aldoxorubicin showed Progression Free Survival (PFS) benefit only in L-sarcoma (liposarcoma + leiomyosarcoma) and is well tolerated with lack of cardiotoxicity [16].

Role of immunotherapy

NY-ESO-1 is highly expressed in MRC-LPS (myxoid round cell liposarcoma) and 80% of SS, and also in other subtypes such as uterine LMS and osteosarcoma [17]. Based on this, a pilot study was conducted with anti-CTLA-4 (cytotoxic T-lymphocyte antigen-4) antibody ipilimumab, in NY-ESO-1 expressing SS. Results showed that ipilimumab was well tolerated with no serious adverse events, even though no objective responses were seen among the six patients treated [18]. In another study which was conducted using NY-ESO-1 engineered T cells, four out of six responses were seen in NY-ESO-expressing SS patients [19].

Tumor-Infiltrating Lymphocytes (TILs) which play an important role in the immune response, has been found in multiple STS subtypes such as LPS, LMS, SS and MPNST. Similar to CTLA-4, the Programmed Cell Death 1 (PD-1) receptor and its Programmed Death Ligand-1 (PDL-1) is another checkpoint molecule. In a retrospective study conducted on STS patients, PD-L 1 expression was found in 100% of patients with epithelioid sarcoma, 53% of SS, 38% of rhabdomyosarcoma, 33% of Ewing sarcoma [20]. A phase II, SARC 028 trial was conducted in patients with 7 different subtypes of pretreated sarcomas to evaluate the effect of Pembrolizumab (Keytruda), PD-1 inhibitor. Treatment with Pembrolizumab resulted in reduction of tumor size in 33% of patients having undifferentiated pleomorphic sarcoma and dedifferentiated liposarcoma [21].

Specific Soft Tissue Sarcoma Subtypes with Unique Treatment Options

Liposarcoma

Liposarcoma is one of the most common soft tissue sarcomas which account for nearly 20% of all adult sarcomas. Based on histology and molecular profile, liposarcomas can be classified into following categories: well/differentiated liposarcoma/atypical lipomatous tumor; dedifferentiated liposarcoma; myxoid liposarcoma; pleomorphic liposarcoma; and liposarcoma, not otherwise specified [22,23] (Table 3,4,5). Due to their heterogeneity and distinct underlying molecular mechanisms that drive growth, liposarcoma subtypes respond variedly to different treatments.

Well-differentiated liposarcoma/Atypical lipomatous tumor: Well differentiated liposarcoma is the least aggressive among

Table 2: Results of phase III study of Aldoxorubicin in soft tissue sarcomas.

Variable	Aldoxorubicin (n= 218)	Investigator's choice(n=215)
ITT(time to death months)		
ORR (total population)	**8.3**	4.2
PFS at 4 months (total population)	**40.8**	31.6
PFS at 6 months (total population)	**24.8**	14.9
DCR (total population)	**30.3**	20.9
DCR (L-sarcoma group)	**37.5**	23
TEAE (grade > = 3 AE)	61	46.4

ORR: Objective Response Rate; PFS: Progression Free Survival; DCR: Disease Control Rate; TEAE: Treatment Emergent Adverse Events [16].

Table 3: Common Cytotoxic Chemotherapeutic Agents Used in Sarcoma [22].

Class	Subclass	Drug	Selected Major Toxicities
Alkylating agents	Platinum agents	Cisplatin	Myelosuppression, nephrotoxicity, ototoxicity, neuropathy
	Nitrogen mustards	Cyclophosphamide	Myelosuppression, cystitis
		Ifosfamide	Myelosuppression, cystitis, CNS toxicity
	Triazines	Dacarbazine	Myelosuppression, gastrointestinal toxicity
		Temozolomide	Myelosuppression
Antimetabolites	Nucleoside analogs	Gemcitabine	Myelosuppression
	Antifolate drugs	Methotrexate	Myelosuppression, mucositis, hepatotoxicity, pneumonitis
Anti-tumor antibiotics	Anthracyclines	Doxorubicin	Myelosuppression, cardiotoxicity, mucositis
	Other	Actinomycin-D	Myelosuppression
Mitotic inhibitors	Taxanes	Docetaxel	Myelosuppression, peripheral neuropathy, edema
		Paclitaxel	Myelosuppression, peripheral neuropathy, hypersensitivity
	Vinca alkaloids	Vinblastine	Myelosuppression, peripheral neuropathy
		Vincristine	Peripheral neuropathy
		Vinorelbine	Myelosuppression, peripheral neuropathy
Topoisomerase inhibitors	Topoisomerase I inhibitors	Irinotecan	Myelosuppression, diarrhea
		Topotecan	Myelosuppression
	Topoisomerase II inhibitors	Etoposide	Myelosuppression

liposarcoma subtypes which accounts for one-third of liposarcomas [24]. Surgery is the main treatment of choice [25,26].

Dedifferentiated liposarcoma: Dedifferentiated liposarcoma has a distant recurrence rate of nearly 30% [27]. Surgical resection is the main treatment modality. Even with aggressive resection, some patients have high rates of local recurrence, but standard chemotherapy regimens are generally ineffective. New treatments regimens using trabectedin or eribulin could be considered in patients with unresectable dedifferentiated or advanced liposarcoma [28].

In a phase II randomized clinical trial, patients with well differentiated/dedifferentiated liposarcoma were treated with palbociclib. The progression free survival at 12 weeks was 57.2 % (95% CI) and the median progression free survival was 17.9 weeks (95% CI). Neutropenia was the most common side effect [29].

Myxoid liposarcoma: Surgery with or without radiation therapy is the common treatment modality. Approximately 40 % of patients experience relapse despite local therapy, and chemotherapy using doxorubicin +/- ifosfamide is a treatment, with reported response rates of just over 40% [30].

In a retrospective study, patients with myxoid liposarcoma treated with trabectedin had a response rate of 50 % (CI 95%) and median progression free survival of 17 months (95% CI) [31].

Other agents in liposarcoma management

CDK_4 antagonists: In well differentiated and dedifferentiated liposarcoma, CDK4 (Cyclin Dependent Kinase 4) is highly expressed, which makes it an attractive target. In-vitro studies with Palbociclib, a CDK4/CDK6 inhibitor induced cell cycle arrest at G1 phase in CDK4 overexpressing liposarcoma cells [32]. A phase II study with palbociclib 125 mg daily for 21 of 28 days in patients with well differentiated and dedifferentiated liposarcomas with CDK4 amplification showed 12-week PFS rate of 66% and low incidence of hematologic adverse events [33].

MDM2 (Murine Double Minute 2 homolog) antagonists: Increased expression of MDM2 has been observed in dedifferentiated liposarcoma. Nutlins, a class of midazoline compounds showed potent activity against MDM2 [34]. A phase I study was conducted in 68 patients with solid malignancies of which 21 patients with dedifferentiated liposarcoma were treated with a maximum tolerable dose of 300 mg/orally/day of SAR405838, an oral spirooxindole derivative that binds MDM2 with high specificity. Results showed stable disease in 11 of 21 patients (52%). Most common adverse events were nausea, fatigue, diarrhoea and thrombocytopenia.

Eribulin: Eribulin is a synthetic macrocyclic ketone derived from marine sponges, which exerts chemotherapeutic effects through unique microtubule dynamics inhibitory effect. In a phase III study,

Table 4: Targeted therapies for sarcomas.

Tumor	Drug and target
Gastrointestinal stromal tumor	TKIs: C-KIT, PDGFR-alpha
Dermatofibrosarcoma Protuberans (DFSP)	Imatinib: PDGFR-beta
Chordoma	Imatinib: PDGFR-beta
Alveolar Soft Parts Sarcoma (ASPS)	Sunitinib and Cediranib: VEGF receptor, MET, RET
Solitary Fibrous Tumor (SFT)	Sunitinib, Bevacizumab + Temozolomide: VEGF, PDGFR, RET
Angiosarcoma	TKIs: VEGF (Taxanes and Doxil)
Pigmented Villonodular Synovitis (PVNS)	Imatinib: COL6A3-M-CSF t(1,6)
Inflammatory Myofibroblastic Tumor	Crizotinib: ALK
Liposarcoma	MDM2 inhibitors: MDM2
Chondrosarcoma	HedgeHog pathway
Perivascular Epithelioid cell Tumor (PEComa)	Everolimus or Temsirolimus: mTOR

Table 5: FDA approved newer drugs for soft tissue sarcoma.

Drug	Year of approval	Indication
Pazopanib	2012	For advanced non-adipocytic soft tissue sarcomas
Trabectedin	2015	Unresectable or metastatic liposarcoma or leiomyosarcoma
eribulin	2016	Unresectable or metastatic liposarcoma
olaratumab	2016	For metastatic soft tissue sarcoma appropriate for anthracycline therapy

Table 6: Liposarcoma Subtype-Specific Treatment Options.

Treatment	ALT/WDLS	DDLS	MRCL	PLS
Chemotherapy	Resistant	Insensitive	Sensitive	Mixed
Doxorubicin ± ifosfamide [3,40]	−*	+	+++	++
Gemcitabine and docetaxel [2]	−	+/−	Unknown	Unknown
Trabectedin [4]	−	+	+++	+
Eribulin [5,48]	Unknown	++†	++†	++†
Palbociclib‡ [16-18]/ LY2835219* [23]	+	++	−	−
First- and second-line treatment failures	CDK4 and MDM2 targeted therapy	CDK4 and MDM2 targeted therapy	Trabectedin	Unknown

ALT: Atypical Lipomatous Tumor; CDK4: Cyclin-Dependent Kinase 4; DDLS: De-differentiated Liposarcoma, MDM2: Murine Double Minute 2; MRCL: Myxoid Round Cell Liposarcoma; PLS: Pleomorphic Liposarcoma; WDLS: Well-Differentiated Liposarcoma.
*The positive (+) and negative (−) symbols in each column represent treatment response by response rate, progression-free survival, or overall survival.
†Overall survival advantage not distinguished for these three subtypes.

patients with liposarcoma or leiomyosarcoma were randomly assigned to eribulin or dacarbazine. The primary end point was overall survival. Results found that patients in eribulin group had overall survival of 13.5 months compared to 11.5 months in dacarbazine group. Subset analysis of patients with liposarcoma showed that patients in eribulin group lived for 15.6 months compared to 8.4 months in dacarbazine group. Due to the significant improvement of 7.2 months, eribulin was approved for the treatment of inoperable and advanced liposarcoma on January, 2016 [35].

Liposarcoma subtype specific management options are shown in Table 6.

Uterine leiomyosarcoma

Leiomyosarcoma accounts for 20% to 25% of STS and may arise from uterus, retroperitoneum and extremities. Uterine sarcomas account for approximately 3% to 7% of uterine cancers. The common subtypes include: 1) Leiomyosarcoma, 2) Endometrial stromal sarcoma, 3) Adenosarcoma, 4) High Grade Undifferentiated Sarcoma (HGUS).

In a phase II study patients with advanced or recurrent leiomyosarcoma received ifosfamide with MESNA (Mercaptoethane Sodium Sulfonate). Results showed partial response in 17.2% patients and grade 3 or 4 granulocytopenia in 11% patients [36].

In another phase II study, patients with advanced, persistent or recurrent uterine leiomyosarcoma were treated with trabectedin. Results showed partial response in 10% patients; stable disease in 50% patients; progression free survival and overall survival of 5.8 months and 26.1 months respectively. Side effects such as neutropenia, thrombocytopenia and anemia were commonly noted [37].

In another phase 2 study, patients with uterine leiomyosarcoma positive for Estrogen Receptor (ER) and Progesterone Receptor (PR) were treated with aromatase inhibitor letrozole. Progression free survival at 12 weeks was 50% and stable disease was found in 54% patients [38].

Gastrointestinal stromal tumors

GIST (Gastrointestinal Stromal Tumors) is a form of soft tissue sarcoma of the gastrointestinal tract. Various mutations have been identified including in KIT gene (exons 9, 11, 13 and 17), PDGFRA (Platelet Derived Growth Factor Receptor Alpha) gene (exons 12,

Table 7: Selected Histology-Specific Chemotherapeutic Regimens in Soft-Tissue Sarcoma [22].

Chemosensitivity	Selected Histology	Selected Conventional Chemotherapy Regimen(s)
Chemo therapy integral to disease management	Ewing sarcoma & Ewing family tumors	VAC/IE VAI VIDE
	Non-pleomorphic rhabdomyosarcoma	VAC VAdriaC VAC/IE IVA
Chemosensitive	Myxoid liposarcoma	doxorubicin, ifosfamide, AIM, trabectedin
	Synovial sarcoma	doxorubicin, ifosfamide, AIM(doxorubicin, ifosfamide, mesna)
	Uterine leiomyosarcoma	gemcitabine, docetaxel + gemcitabine, docetaxel + doxorubicin API(doxorubicin, cisplatin, ifosfamide)
Intermediate chemosensitivity	Angiosarcoma	paclitaxel, gemcitabine, doxorubicin
	Desmoplastic small round cell tumor (DSRCT)	P6 protocol +/− thiotepa, carboplatin and SCT
	Desmoid, aggressive fibromatosis	methotrexate + vinblastine, doxorubicin +/− dacarbazine
	Leiomyosarcoma	doxorubicin +/−dacarbazine, trabectedin, gemcitabine + docetaxel
	MPNST	IA/IE
	Myxofibrosarcoma	doxorubicin, AIM
	Pleomorphic liposarcoma	doxorubicin, AIM, doxorubicin + dacarbazine
	Pleomorphic rhabdomyosarcoma	doxorubicin, AIM, VAI
	Undifferentiated pleomorphic sarcoma	doxorubicin, AIM
Relatively chemoresistant	Chondrosarcoma	cyclophosphamide + sirolimus
	Solitary fibrous tumor	temozolomide + bevacizumab, TKLs(Sunitinib/ Sorafenib)
	Well- or dedifferentiated liposarcoma	doxorubicin, AIM, doxorubicin + dacarbazine, palbociclib

VAC/IE: Vincristine, Doxorubicin, Cyclophosphamide alternating with Ifosfamide, etoposide; VAI: Vincristine, Doxorubicin, Ifosfamide; VIDE: Vincristine, Ifosfamide, Doxorubicine, Etoposide; VAC: Vincristine, Actinomycin D, Cyclophosphamide; VAdriaC, Vincristine, Doxorubicin, Cyclophosphamide; IVA, Ifosfamide, Vincristine, Dactinomycin; MAP: Methotrexate, doxorubicine, cisplatin; AP: Doxorubicin, Cisplatin; AIM: Doxorubicin, Ifosfamide, MESNA; API: Doxorubicin, Cisplatin, Ifosfamide; P6 protocol, Cyclophosphamide, Doxorubicin, Vincristine, Ifosfamide, Etoposide; SCT: Stem-Cell Transplant; IA/IE: Ifosfamide, Doxorubicin followed by Ifosfamide, Etoposide.

Table 8: Proposed treatment sequence for advanced or metastatic, high-grade soft tissue sarcoma [66].

Sarcoma subtype	First line	Second line	Third line	Fourth line
UPS	[a]Anthracycline-based regimen	Gemcitabine + docetaxel	Pazopanib	PDL-1
LPS	[a]Anthracycline-based regimen	[b]Trabectedin or eribulin	Eribulin or trabectedin	
LMS	[a]Anthracycline-based regimen	[c]Gemcitabine + docetaxel	Trabectedin	Pazopanib
SS	[a]Anthracycline-based regimen	[d]High-dose ifosfamide	Pazopanib	
MPNST	[a]Anthracycline-based regimen	Pazopanib		

[a]Anthracycline-based regimens include: single-agent doxorubicin, doxorubicin and ifosfamide, doxorubicin and olaratumab, or liposomal doxorubicin.
[b]Trabectedin particularly effective for myxoid/round cell LPS.
[c]Gemcitabine + docetaxel particularly effective for uterine LMS.
[d]High-dose ifosfamide only recommended for select patients with good performance status and preserved renal function.
[e]Clinical trials are recommended for eligible patients.
UPS: Undifferentiated Pleomorphic Sarcoma; LPS: Liposarcoma; LMS: Leiomyosarcoma; SS: Synovial Sarcoma; MPNST: Malignant Peripheral Nerve Sheath Tumor.

14 and 18). About 10% to 15% of gastrointestinal stromal tumors carries wild type sequences in all hot spots of KIT and PDGFRA and hence called as wild type GISTs. The Carney-Stratakis syndrome comprising of hereditary GIST and paraganglioma is a result of germ line mutation in the mitochondrial tumor suppressor gene pathway involving the Succinate Dehydrogenase (SDH) subunits SDHD, SDHC and SDHB.

The treatment of GI stromal tumors may include combination of surgery with or without systemic therapy, either in neo-adjuvant or adjuvant setting. The decision regarding need for systemic therapy is based on the risk stratification for recurrence. Three tyrosine kinase inhibitors have been approved for treatment including Imatinib, Sunitinib and Regorafenib.

Retroperitoneal sarcoma

Retroperitoneal Sarcomas (RPSs) are rare tumors that account for nearly 15% of STSs [39]. The most common histologic subtypes are Well or Dedifferentiated Liposarcoma (WDLPS or DDLPS), leiomyosarcoma, synovial sarcoma, undifferentiated pleomorphic sarcoma and malignant peripheral nerve sheath tumors [40]. The most common treatment for RPSs is primary resection.

A retrospective analysis to evaluate the effect of adjuvant radiotherapy found 3 year local recurrence rate was 49% in surgery alone group and 34% in surgery plus radiotherapy group. However limited data is available about role of adjuvant chemotherapy in the management of RPSs [41].

In a prospective trial patients with surgically resected sarcomas of the retroperitoneum were randomly assigned to receive post-operative high dose radiotherapy alone or Intraoperative Radiotherapy (IORT) in combination with low dose post-operative external beam radiotherapy. Results showed comparable median survival time in both groups (45 vs. 52 months). In patients who received IORT, there was lower incidence of loco-regional recurrences (6 of 15 (40%) vs. 16 of 20 (80%)), fewer complications of disabling enteritis (2 of 15 vs. 10 of 20) but a higher frequency of radiation related peripheral

neuropathy (9 of 15 Vs 1 of 20) [42].

In a case control, propensity score matched analysis; overall survival was assessed in patients with retroperitoneal sarcomas who received preoperative radiotherapy, postoperative radiotherapy and no radiotherapy. Results showed overall survival of 110 months in preoperative group versus 66 months in patients who did not receive radiotherapy (p <0.0001, 95% CI) and 89 months in postoperative group versus 64 months in patients without radiotherapy (p <0.0001, 95% CI) [43].

Angiosarcoma

Angiosarcomas are unusual malignant tumors of endothelial origin with high propensity for metastatic disease and in general with poor prognosis.

For localized tumors, radical surgical resection is the primary treatment option. Because of the high risk of local recurrence, adjuvant radiotherapy +/- chemotherapy is recommended.

In a retrospective study, 9 patients with cutaneous angiosarcoma received docetaxel. 2/9 patients showed complete response and 4/9 patients showed partial response. 3/9 patients experienced severe dermatitis; with no significant incidence of neutropenia and peripheral neuropathy [44].

In a phase II trial, patients with metastatic or unresectable angiosarcoma were treated with paclitaxel. Results showed progression free survival of 74% and 45% after 2 and 4 months respectively. Median time to progression was 4 months and median overall survival was 8 months. Anemia and fatigue were the most toxicity [45].

In another phase II trial, 32 patients with advanced angiosarcoma were treated with bevacizumab. Two patients had partial response; 11 with stable disease and meantime to progression were 26 weeks. One patient had graded 4 adverse events [46].

Kaposi sarcoma

Kaposi Sarcoma (KS) is an angioproliferative malignancy that occurs most often due to infection with Human Herpes Virus 8 (HHV-8) and classified into 4 types: Classic; endemic; iatrogenic; AIDS associated [47].

Management: In a prospective clinical trial, topical Imiquimod showed objective response (complete or partial) in 47 % patients [48].

Data from case series showed regression of cutaneous Kaposi sarcoma lesions with topical timolol [49].

Nitrogen cryotherapy and laser therapy have been used for local control of small CKS (Classic Kaposi's Sarcoma) lesions [50].

Intralesional therapy: Intralesional injection using chemotherapeutic agents (commonly vinblastine, bleomycin) causes local regression of cutaneous KS lesions [51]. Intralesional injection using Interferon Alfa (IFNa), alone or in combination with interleukin-2, has also shown regression of CKS lesions [52].

Electrochemotherapy using small electric current (electroporation, a form of electromotive drug administration) enhances drug delivery into the tumor. This has been mostly used with bleomycin. In a study conducted on 23 patients with CKS treated using this approach, results showed tumor regression in all patients with complete regression seen in 65% [53].

A prospective study was conducted in 21 HIV infected subjects (with associated Kaposi sarcoma) to evaluate the effect of Highly Active Antiretroviral Therapy (HAART) on circulating Kaposi Sarcoma (KS) associated Herpes Virus (KSHV) load in HIV infected individuals. 10/21 patients showed favorable Kaposi sarcoma response (Complete response: 6; partial response: 4) with HAART alone. 60% of patients had an undetectable KSHV load with antiretroviral therapy. No significant difference between subjects receiving protease inhibitors or non-nucleotide reverse transcriptase inhibitor based treatment combination was noticed [54].

In a retrospective study pretreated patients with aggressive, non-visceral classic Kaposi sarcoma received pegylated liposomal doxorubicin. Complete and partial responses were noticed in 10% and 70 % of patient population. 20% of patients developed neutropenia. Median progression free survival was 9 months (95 % CI); at a median follow up of 36 months 75% patients remained alive [55].

Dermatofibrosarcoma protuberans

Dermatofibrosarcoma Protuberans (DFSP) is an uncommon, low grade STS which originates from cutaneous mesenchymal cells. It is characterized by slow growth with low rates of invasion and most commonly occurs in the 20 to 50 years age group. The most common mechanism involved in the pathogenesis of dermatofibrosarcoma is rearrangement of chromosome 17 and 22, leading to activation of Platelet Derived Growth Factor (PDGF), which acts as a stimulus for tumor growth.

The most common treatment modality is complete surgical resection with microscopically negative margins. For locally unresectable/metastatic DFSP, tyrosine kinase inhibitor, imatinib has been approved for treatment. This is based on a phase II trial with imatinib 400 vs. 800 mg in patients with locally advanced or metastatic DFSP. This showed Objective response rate of 50% in imatinib group. There was no significant difference in response rate and Time To Progression (TTP) between 400 mg vs. 400 mg dosing [56,57].

Alveolar soft part sarcoma

Alveolar soft part sarcoma is a rare malignancy which accounts for 0.8% of STS. It usually arises in soft tissue or bone mostly affecting patients younger than <35 years. Due to the extreme vascular nature of the tumor, early metastasis, frequently at the time of presentation is common [58].

In a phase II trial, cediranib, a VEGFR (Vascular Endothelial Growth Factor Receptor)-1,2, 3inhibitor, showed 35% objective response rate and disease control rate of 84% at 24 weeks [59].

In another study, Sunitinib, a TKI (Tyrosine Kinase Inhibitor) with anti VEGF activity showed median progression free survival of 19 months with 86% patients being free of progression at 6 months. Median overall survival was 56 months. Most common toxicities were neutropenia, thrombocytopenia, hypothyroidism and arterial hypertension [60].

Newer approaches with immune check point inhibitors, targeted drug combinations and tumor vaccines are active in this subtype of sarcoma [61].

Dendritic cell and histiocytic sarcoma

Hematopoietic tumors originating from CD 34 + myeloid progenitor cells include Histiocytic Sarcoma (HS), Langerhans Cells

Histiocytosis/Sarcoma (LCH) and Interdigitating Dendritic Cell Sarcoma (IDCS), whereas stromal or mesenchymal derived tumors include Follicular Dendritic Cell Sarcoma (FDCS) and fibroblastic reticular cell tumors.

A retrospective analysis was conducted on patients with FDCS, IDCS, and HS to evaluate the impact of surgery, radiation and systemic therapies on overall survival. Results showed that with surgical management, patients with localized disease had significant improvement in overall survival than those with metastatic disease in FDCS (p =0.04) and IDCS (p =0.014) but no significant difference in HS group (p =0.95). Adjuvant radiotherapy and neo adjuvant chemotherapy with doxorubicin and ifosfamide regimens did not show significant improvement in overall survival. In IDCS, a 5 year overall survival rate of 71 % was noted with surgery alone [62].

For localized FDCS, surgical resection is the treatment of choice. Analysis of 66 patients with advanced FDCS showed an overall response rate of 80% in 10 patients who received gemcitabine and a taxane (2 complete responses); and the median response duration was 13.4 months (range 3 to 83 months). Partial responses were noticed in 3 patients who received ifosfamide and doxorubicin based regimens and in one of the 2 patients who were treated with an anthracycline based regimen (CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone) [63].

Peritoneal sarcomatosis in pediatric malignancy

Peritoneal Sarcomatosis (PSC) is characterized by peritoneal involvement of multiple sarcomatous tumors. The most common pediatric PSC are seen in Desmoplastic Small Round Cell Tumors (DSRCT) and rhabdomyosarcoma. Chemotherapy and palliative surgery are the common treatment practices, but long-term outcomes were poor.

Some of the newer treatment modalities such as Cytoreductive Surgery (CRS) followed by Hyperthermic Intraperitoneal Chemotherapy (HIPEC) have resulted in prolonging remission in pediatric population [64].

Results from a prospective database of patients who underwent CRS/HIPEC showed that median intraabdominal disease free and overall survival after CRS/ HIPEC were 17.2 (95% CI: 2.4 - 19.7) and 22.6 months (95% CI: 6.1 - 62.6 months) respectively. The recurrence rate with CRS/ HIPEC Vs CRS only was 17.2 Vs 10.7 months (p =0.52) [65].

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