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Targeted Therapy of Soft Tissue Sarcoma: There is More than one Way to Skin a Cat!

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Abstract

Soft tissue sarcomas are an uncommon and diverse group of more than 50 mesenchymal malignancies with very specific underlying molecular events driving oncogenesis. The mysterious pathogenesis is slowly revealing the vary secrets of their inner workings. There is a paradigm shift in sarcoma management wherein therapeutic decision-making is guided by key genetic events of oncogenic potential. Present perspective, will focus on the rationale for targeted delivery of therapy in sarcoma, with emphasis on the relevance of specific molecular factors and pathways. It will also focus upon the story behind some of the early successes and challenges and disappointments in taming these targets. Finally it will discuss possible opportunities represented by poorly understood, but potentially promising new therapeutic targets and investigational biological agents. This communication will provide a demarche of the current state of the art for medical management of sarcomas and a sense of where it may be headed in the coming years.

Keywords: Biological agents; Pathogenesis; Sarcoma; Specific molecular

Introduction

Sarcomas represent a family of rare cancers of bone and soft tissue accounting for less than 1% of cancer in adults and approximately 15% of pediatric cancer [1]. They are biologically heterogeneous, with more than 50 histologic subtypes identified in soft tissue and more than 20 in bone, in keeping with the multiple types of connective tissue that constitute the human body [2]. Although outcomes vary greatly by sarcoma subtype, current therapies are limited and urgent need for more effective therapies is reflected by persistently poor five year sarcoma survivals of approximately 50% [3]. Being rare, sarcomas may represent ideal targets for the experimental drug discoveries. Further, unlike most of the common cancers which are driven by a wider array of molecular events [4], these rare tumors may be driven by a single genetic event, and rely on this aberration to survive (oncogenic addiction). This theory has been borne out in some sarcomas, most notably gastrointestinal stromal tumor (GIST) and dermato fibro sarcoma protuberans (DFSP), in which targeted agents have had a high degree of treatment success. Other sarcomas governed by complex molecular events are yet to be explored for determining specific targets.

Sarcoma molecular pathogenesis

Sarcomas are broadly classified by underlying genomic events as 1) those with specific translocations or gene amplification, 2) those with defining oncogenic mutations and 3) those with complex genomic rearrangements. Each class contains whole spectrum of tumors with a wide array of clinical, histological and molecular characteristics (Table 1).

Translocation-associated sarcomas

Currently, specific, recurrent translocations have been identified in 19 soft tissue sarcomas. Translocation associated sarcomas account for 20-30% of all sarcomas [5], and this number are growing larger with new discoveries of recurrent translocations in additional tumor types. These recurrent translocations result in chimeric fusion genes which function as transcription factors, as is epitomized by the *EWSR1-FLI1* fusion gene in Ewing sarcoma. Less commonly, it results in over expression or constitutive activation of a growth factor receptor tyrosine kinase (RTK) or other chimeric growth factor signalling protein. This event is seen in DFSP, in which wild types PDGFB is overexpressed under the COL1A1 promoter, and inflammatory myofibroblastictumor (IMT) in which ALK fusion protein promote dimerization of the ALK tyrosine kinase thereby rendering it constitutively active [6,7].

Amplification-associated sarcomas

Recurrent amplifications have identified only in a few soft tissue sarcomas, most notably well-differentiated or dedifferentiated liposarcomas, in which amplification of chromosome 12q13-15, including HDM2 (MDM2) and CDK4 is characteristic [8]. HDM2 functions as an inhibitor of p53. Accordingly, amplification and subsequent overexpression of this chromosomal locus results in inhibition of p53-dependent cell-cycle arrest and apoptosis. Cdk4 is a cell cycle regulator, and over expression of this factor promotes proliferation, while other gene loci within this interval may also have pro-oncogenic effects.

MYC amplification has been identified in secondary (radiation-induced) angiosarcoma [9], and may be seen sporadically in other sarcomas [10-12]. MYC is a proto-oncogenic transcription factor, which can act as either a transactivator or repressor, and has been reported thus far in many cancers [13,14].

Selected approved targeted agents in sarcoma				
Sr. no.	Agent	Target	Tumor	Status
	Tyrosine Kinase Inhibitors			
1	Imatinib mesylate	Kit, Abl, PDGFR	GIST, DFSP	FDA Approved
2	Sunitinib	Multiple tyrosine kinases: PDGFR, Kit, RET, CSF-1R, Flt3, VEGFR	GIST	FDA Approved
3	Regorafenib	Multiple tyrosine kinases: RET, VEGFR, KIT, PDGFR-alpha, FGFR, TIE2, DDR2, Trk2A, Eph2A, RAF-1, BRAF, SAPK2, PTK5	GIST	FDA Approved
4	Pazopinib	VEGFR, PDGFR, Kit	STS (except liopsarcoma and GIST)	FDA Approved
5	Sirolimus	mTOR inhibitor	Lymphangomyomatosis	FDA Approved

Table 1: Sarcoma Targeted Agents (Established).

Pediatric sarcomas

The most common histologic varients of sarcoma seen in paeditric age group include Osteogenic sarcoma, Ewing sarcoma, Rhabdomyosarcoma (alveolar and embryonal subtypes, primarily), and less commonly nonrhabdomyosarcoma group of tumor (synovial sarcoma and desmoplastic small round cell tumor). There is less than handful of agents in armamentarium to treat each of these tumors (Table 1) (Figure 1).

Rhabdomyosarcoma

Rhabdomyosarcoma most commonly affect children under 5 years of age; however they are also seen in adolescents and young adults. The tissue of origin is skeletal muscle and there are 2 major histologic subtypes, alveolar (ARMS) and embryonal (ERMS). ARMS are characterized by translocations between the DNA-binding domain of either PAX3 or PAX7 and the transactivation domain of FOXO1. ARMS are more comon in older children adolescents, and young adults and their prognosis is poorer than ERMS. Similar to Ewing sarcoma, preclinical and clinical data suggested important role of IGF signaling in rhabdomyosarcoma. Both alveolar and embryonal rhabdomyosarcoma have high expression of IGF-II and IGF1R through diverse mechanisms. Loss of imprinting at IGF2 locus is present in ERMS. The fusion transcription factor PAX3-FOXO1 targets the IGF1R promoter [15]. According to a phase 2 trial, the combination of cixutumumab and temsirolimus had clinical activity in patients with sarcoma however; IGF-1R expression by immunohistochemistry was not predictive of clinical outcome [16].

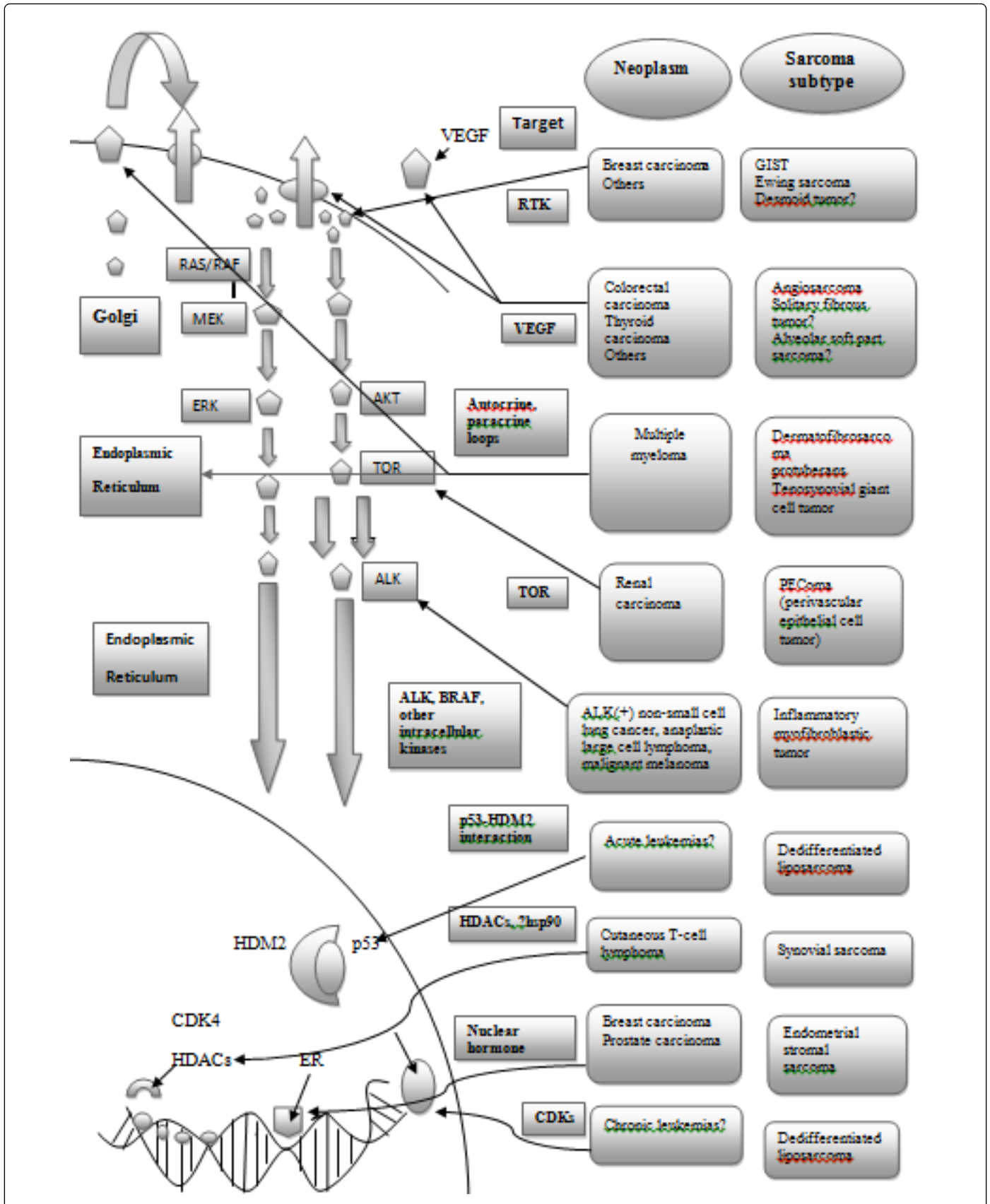

Figure 1: Sarcoma targeted agents (Established).

Inflammatory myofibroblastic tumor

Inflammatory myofibroblastic tumor (IMT) is a rare, locally aggressive tumor. It is a neoplasm composed of myofibroblastic and fibroblastic spindle cell proliferation associated with inflammatory infiltrate of plasma cells, lymphocytes and/or eosinophils. It is biologically heterogeneous but was found to harbor translocations involving ALK in 50% of patients, particularly younger patients [17,18].

ALK, encoded by its cognate gene located on chromosome 2 (2q23), is a receptor tyrosine kinase that belongs to the insulin receptor family [19,20]. Normally its expression is limited to the central and peripheral nervous system where it promotes cell proliferation, survival and differentiation in response to extracellular stimuli by activating the PI3/AKT, MAPK/ERK and STAT3 pathways [20]. *ALK* gene abnormalities are also identified in other tumors such as neuroblastoma, lung carcinoma, rhabdomyosarcoma, renal cell carcinoma and inflammatory breast cancer [20-22]. Crizotinib is a small-molecule inhibitor of anaplastic lymphoma kinase (ALK). IMT being rare tumor activity of crizotinib is difficult to document in randomized trials; however, phase I studies in adults [23], and children [24,25] shown activity in this tumor type.

Adult onset sarcomas

Sarcomas are comparatively more uncommon in adults than other cancers and are more heterogeneous. Sarcoma subtypes can be differentiated based on anatomic primary site and patient age. GIST, UPS, leiomyosarcoma, and the 3 forms of liposarcoma are the most common subtypes in adults. However, childhood predominating sarcomas may present in adults with atypical presentations. Ewing sarcoma is a common bone tumor in children, but is predominantly a primary soft tissue sarcoma in adults; rhabdomyosarcoma is mainly the pleomorphic subtype in adults than in children in who membryonal and alveolar are commonest subtypes.

Despite their heterogeneity, over the last several years a variety of novel agents have been found to be active in specific sarcoma subtypes. These are outlined in Table 2; and are described comprehensively later. Adult sarcomas are likewise challenging as pediatric sarcomas however, for some specific types there are sufficient numbers of patients to complete randomized clinical trials.

Investigational targeted agents in sarcoma

Sr. no.	Agent	Target	Tumor	Status
	Tyrosine Kinase			
	Inhibitors			
1	Sorafenib	Multiple	Angiosarcoma, solitary	Phase II [115]
		kinases: Kit,	fibrous tumor/	
		VEGFR,	hemangiopericytoma,	
		PDGFR, Raf	alveolar soft	
			part sarcoma, clear cell	
			sarcoma	
2	Imatinib	Kit, Abl,	Tenosynovial giant cell	Retrospective
		PDGFR	tumor/pigmented	analysis of
			villonodular synovitis	Data [101]
3	Crizotinib	Alk/ Met	IMT	Phase I [116]
	Met Inhibitor			
4	Tinvatinib	Met	Alveolar soft part	Phase II [99]
			sarcoma	
	mTORC1 Inhibitors			
5	Ridaforolomus	mTORC1	Metastatic Soft tissue	Phase
	(deferolimus)		sarcoma	Phase I, III [119]
	Anti-Angiogenic Agents			
6	Bevacizumab	VEGFR	Angiosarcoma, solitary	Phase II [114]
			fibrous tumor/	

			hemangiopericytoma,	
			alveolar soft	
			part sarcoma, clear cell	
			sarcoma	
7	Cediranib	VEGFR	Angiosarcoma, solitary	Phase I [118]
			fibrous tumor/	
			hemangiopericytoma,	
			alveolar soft	
			part sarcoma, clear cell	
			sarcoma	
	Anti PDGFR			
8	Olartumumab	PDGFR-α	Metastatic STS	Phase II [118]
	Epigenetic Modifier			
	Inhibitor			
9	Vorinostat	HDAC	Synovial sarcoma	Phase II [119]

Table 2: Sarcoma targeted agents (Investigational).

Gastrointestinal stromal tumor

GIST is a mesenchymal tumor showing differentiation toward the interstitial cells of Cajal and may actually arise from this lineage or a precursor [26]. Risk assessment for GIST using the NIH/NCCN/ Miettinen criteria are of therapeutic importance especially in deciding for adjuvant imatinib therapy for higher risk localized tumors. These criteria are quite different from the traditional French (FNCLCC) grading system in which site and size of the tumor rather than mitotic activity (indicator of aggressiveness of the tumor) are important.

The KIT receptor is important for normal development and function of the interstitial cells of Cajal, hematopoiesis, gametogenesis and melanogenesis [27-30] Constitutive activation of KIT (4q12~13) or occasionally PDGFRA tyrosine kinase by oncogenic mutation plays a key role in GIST pathogenesis [31,32]. In GIST, most of the mutations (70-75%) involve the juxtamembrane domain of the KIT receptor, in a hot spot region at the 5' end of exon 11 (codons 550- 560) [27,33,34]. These mutations cause constitutive activation through loss of the KIT negative regulatory functions .These commonly seen KIT mutations in exon 11 are not associated with a specific clinicopathologic phenotype. However, deletion mutations, specifically those affecting codons 557 and 558, are harbinger of more aggressive clinical course than substitution mutations [35-37]. Interestingly, tumors with ITDs at the 3' end of exon 11 are often associated with more indolent gastric tumors [34,38].

KIT mutations affecting exon 9 occur in 10-15% of cases. They are aggressive, small bowel tumors and respond better to escalated doses of imatinib [34,39]. About one-third of GISTs that lack KIT mutations harbor mutations in PDGFRA (exons 12, 14 or 18) [33,40,41]. These tumors tend to be of epithelioid morphology, gastric origin and indolent behavior [41,42]. Approximately 10% of patients do not show evidence of mutations in either KIT or PDGFRA and are often termed "wild-type" GIST. These are seen particularly in pediatric patients or in association with neurofibromatosis type 15 [43-45].

GIST is diagnosed on the morphologic features and reactivity with KIT (CD117) and DOG1 by immunohistochemistry. However, about 4% of cases are negative for KIT by immunohistochemistry (KIT negative GIST) [46]. The diagnosis in such cases should be supported by ruling out other differential diagnoses such as smooth muscle neoplasms, neural tumors and fibrous tumors. Molecular tests to detect mutations in KIT or PDGFRA would be another adjunct to support the diagnosis since KIT immunonegative GIST cans still harbor mutations in these genes. The rate of response to imatinib treatment varies depending on the type of mutation, as patients with KIT exon 11 mutations have a much higher chance for response (84%) than wild-type GIST (5%), and tumors with exon 9 mutations may require a higher dose of imatinib for equivalent response [27,47]. GIST remains the best example of a sarcoma in which the use of a kinase-directed agent led to impressive clinical results [48]; notably for the first time a survival advantage was shown for use of imatinib in the adjuvant setting [49]. Patients who received 3 years of imatinib had improved 5-year survival as compared with patients who received only 1 year of therapy. In metastatic setting, early assessment of treatment response provides the opportunity to shift to an alternative therapy (e.g., resection or sunitinib) if imatinib is ineffective. For those patients who develop resistance to both imatinib and sunitinib, regorafinib is indicated.

Another metabolic pathway genetic alteration which leads to a form of GIST that occurs predominantly in children and young adults is called “succinate dehydrogenase (SDH)-negative" form of GIST. In this form, loss of SDH expression is observed, and may ultimately provide new means to treat both these so-called "pediatric," syndromic GISTs, and much more common KIT or PDGFRA mutant GIST [50,51]. Others may show smooth muscle or rhabdomyogenic differentiation

on rare occasion [52]. About 50% of resistant tumors do not show evidence of secondary mutation which suggest other mechanisms of resistance such as KIT genomic amplification and activation of alternative receptor tyrosine kinase protein in the absence of KIT expression [27,53]. Often multiple mechanisms of resistance are seen with multifocal recurrence during therapy and this has limited the clinical utility of KIT genotyping in the setting of resistance.

Synovial sarcoma

Synovial sarcoma is role-model wherein a specific SS18-SSX translocation product drives the phenotype of this cancer. Monophasic and biphasic varieties of the cancer develop based on the SS18-SSX subtype [54]. The cell of origin was suggested to be the satellite cell of skeletal muscle, based on the context-dependent tumor growth seen when the same transgene was introduced into different cell types [55]. It was found that Hsp90 inhibitors and histone deacetylase (HDAC) inhibitors could be a useful option for this sarcoma subtype [56-59]. Gene knockdown or an HDAC inhibitor decreases synovial sarcoma growth and causes apoptosis. These studies highlighted importance of clinical trials using HDAC inhibitors in synovial sarcoma. The relative lack of overlapping toxicity of HDAC inhibitors with cytotoxic agents or kinase-directed agents has definitive advantage of using them in combination.

Well differentiated-dedifferentiated liposarcoma (WD–DD LS)

This is one of the most common and most frustrating diagnoses that often occurs in the abdomen/retroperitoneum and notorious for relapses and remissions ultimatly leading to deaths typically from local disease progression rather than distant spread. Overall 8% of DD LS were detected to have mutations in HDAC1 [60]. It suggest for other epigenetic mechanisms by which WD–DD LS requires to survive with several copies of the same sequencing encoding HDM2, CDK4, and neighboring genes on chromosome 12q [61].

These data emphasizes the major role of amplification of chromosome 12q [62]. This characteristic amplification brings into focus the use of human homologue of murine double minute 2 (HDM2) or cyclin-dependent kinase 4 (CDK4) inhibitors in this form of liposarcoma [63]. These tumors can be very genetically complex, but they all have amplifications of the long arm of chromosome 12. There are 2 specific amplicons: one is centered at cyclin-dependent kinase 4 (CDK4) and one is centered at MDM2. CDK4 and MDM2 may play a role in the propagation and pathogenesis of these tumors, thus this has led to the use of selective CDK4 inhibitors and selective MDM2 inhibitors.

Patients who have progressing disease can achieve SD when a drug such as the CDK4 inhibitor palbociclib is used, can actually achieve stable disease. There is a group of patients with these sarcomas that can progress quickly through treatment, but there also is also a group of patients that can have dramatic responses, sometimes complete responses (CRs), and can also be on a drug for multiple years. The extremes of responses in this patient population has now allowed for the potential identification of pretreatment biomarkers that may be able identify patients who will have dramatic responses and those who do not respond to these therapies.

Dermatofibrosarcoma protuberance (DFSP)

DFSP is a mesenchymal spindle cell neoplasm charactersed by high propensity for local recurrence and low risk for distant dissemination. However, fibrosarcomatous differentiation confers a metastatic rate of 15 to 20% in DFSP.

DFSP is characterized by a translocation of chromosomes 17 and 22 t (17; 22)(q22; q13) or the formation of supernumerary ring chromosomes which exhibit contributions from chromosomal regions 17q22 and 22q13, leading to the fusion of collagen 1 alpha 1 (COL1A1) on chromosome 17 with platelet-derived growth factor-B (PDGFB) [64,65]. This results in transcriptional up regulation of *PDGFB* gene in the form of COL1A1-PDGFB fusion [66]. The *PDGFB* gene product is a growth factor that acts as a ligand for the transmembrane receptor kinase PDGFRB [67]. The post transcriptional fusion protein is capable of inducing activation of its receptor through autocrine and paracrine routes resulting in the propagation of a pro tumorigenic signal [68-70].

Imatinib interferes with PDGFRB signaling pathway by competing with adenosine triphosphate (ATP) binding and consequently preventing the tyrosine kinase receptor autophosphorylation and downstream pathway activation [67]. *In vitro* data [71,72] as well several case series and case reports showed good response to imatinib treatment in locally advanced and metastatic DFSP [73-79]. DFSP with fibrosarcomatous transformation (DFSP-FS) also respond to Imatinib although the responses may be less durable. DFSP-FS with no detectable translocation t (17;22) had shown no response to imatinib and could represent either misdiagnoses or mediated through unknown alternative pathways not responsive to imatinib [79]. Therefore, molecular testing can accurately predict likelihood of response to Imatinib. Majority of DFSP is treated with local surgical extirpation; imatinib is indicated in locally advanced/non resectable tumors, metastatic/recurrent disease and as neoadjuvant therapy to decrease the morbidity of surgery [67].

Perivascular epithelioid cell tumors (PEComas)

PEComas are a group of related mesenchymal neoplasms that exhibit myomelanocytic differentiation [80-82]. They have a unique immunohistochemical profile that includes reactivity to both melanocytic markers (HMB45 and/or Melan-A) and smooth muscle markers (actin and/or desmin). PEComas include angiomyolipoma (AML), lymphangiomyomatosis (LAM), clear cell sugar tumor and perivascular epithelioid cell tumor-not otherwise specified (PEComa-NOS) [83]. These tumors are rare and usually arise sporadically, however, LAM and AML are seen at high frequency with tuberous sclerosis complex (TSC) [84]. They are generally benign and recurrence after complete surgical resection is exceptional; however, a subset exhibits more aggressive and malignant behavior with locally invasive recurrences and/or distant metastasis [84]. It was found that there is a germline loss of heterozygosity (LOH) at the TSC2 locus in TSC-associated AML and LAM; TSC2 also seems to be more commonly lost in sporadic cases than TSC1 [85-88]. These two tumor suppressor genes (*TSC1* and *TSC2*) encode proteins that have a role in regulating cell proliferation via the Mtorpathway [89]. Theraputic evidence of mTOR inhibitors were shown in AML and LAM [90-92]. Several case seriesand case reports have shown promising responses with at least one case showing long term control (16 months), though these tumors are not uniformly responsive [84,93,94]. In view of lack of benefit of the traditional cytotoxic treatment in metastatic PEComa, mTOR inhibitors should be considered in any patient with recurrent or

metastatic disease [83]. Based on above data Sirolimus is approved in the United States for treatment of pulmonary LAM.

Alveolar soft part sarcoma (ASPS)

ASPS is a relatively indolent variety of soft tissue sarcoma driven by an unbalanced translocation between the chromosomes X and 17 (X; 17)(p11;25) resulting in fusion of ASPS critical region-1 gene (*ASPSCR1*) located on chromosome 17q25 and the transcription factor for immunoglobulin heavy chain enhancer 3 (*TFE3*) gene located on chromosome Xp11.2269. The result of this gene rearrangement is one of two novels functional ASPSCR1-TFE3 fusion proteins [94] induce strong overexpression of the MET receptor tyrosine kinase gene in ASPS cells [95]. In the presence of its ligand, hepatocyte growth factor, the MET receptor tyrosine kinase undergoes strong autophosphorylation, activating downstream signaling of the MAP kinase and PI3K/Akt pathways [95].

Diagnosis of ASPS is made based on its characteristic microscopic appearance, with immune histochemical study to detect TFE3 nuclear expression and molecular techniques to detect gene rearrangement in difficult cases [96]. Although, the best treatment modality of ASPS is surgical resection is not feasible in advanced/metastatic disease wherein chemotherapy and radiotherapy are also not very effective [94,97]. Therefore, targeted therapy is an attractive option with its advantages of less toxicity and daily outpatient use. Inhibition of the overexpressed MET could be a potential target to decrease the cell growth in such tumors. Other targetable molecules include MDK (midkine or neurite growth-promoting factor-2) and Jag-1 (Jagged-1) which is regulators for angiogenesis and both shown to be over expressed in ASPS [98]. Tivantinib, a selective inhibitor of the Met receptor tyrosine kinase, showed modest response and was tolerable and safe for patients [99].

PVNS and GCT-TS

Patients with this disease can have collagen deposition, subchondral bone erosions, and repeat hemarthrosis, which can actually be very destructive to the joint and the bones. This usually causes significant swelling, pain, decreased range of motion, and often can cause functional impairment and the reliance on narcotics. Although this may not threaten the patient's life, it can definitely change the trajectory of the patient's life and cause a significant amount of morbidity. The discovery of this translocation in the overexpression of colony-stimulating factor 1 (CSF-1) led to the use of specific CSF-1 inhibitors that were available to us in the clinic in this setting [100]. A retrospective analysis pooling data showed that the use of the CSF-1 inhibitor, imatinib mesylate, provided some modest responses [101]. Other stronger specific CSF-1 inhibitors are under investigation in this setting, such as pexidartinib, which is a CSF-1 and KIT inhibitor (Table 2).

Promising newer agents

Trabectedin: Trabectedin was originally isolated from the sea sponge *Ecteinascidia turbinate*, acts by interfering with the deoxyribonucleic acid (DNA) nucleotide excision repair machinery [102]. Trabectedin is an active agent for advanced STS, although the objective response rate, by conventional criteria, is fairly low [103-107]. Highest response rates were in the myxoid/round cell liposarcoma and leiomyosarcoma subtypes. Trabectedin was approved in the United States for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who have received a prior anthracycline-containing regimen [108]. High response rate has been seen in patients with advanced pretreated myxoid/round cell liposarcoma (MRCL); in one study of 51 such patients, 51% had either a complete or partial response, and 88% were progression-free at six months [109]. The benefit of trabectedinin this subtype is in concordance with clinical activity reported in patients with the "translocationrelated"sarcomas [110].

Pazopanib: Pazopanibis a multitargeted, orally active, small molecule inhibitor of several TKs. Single agent pazopanib showed activity in a phase II clinical trial that included various STS subtypes [111]. Pazopanib met the primary endpoint for activity in leiomyosarcomas, synovial sarcomas, and other STS types, but not liposarcoma. A worldwide, randomized, double-blinded, phase III study (the PALETTE trial) compared pazopanib (800 mg daily) versus placebo in 369 patients with a variety of histologic subtypes (leiomyosarcoma, fibrosarcoma, synovial sarcoma, malignant peripheral nerve sheath tumor [MPNST], vascular STS, sarcoma not otherwise specified, but not adipocytic sarcomas or GIST) whose disease had progressed during or after first-line chemotherapy [112]. The median PFS was significantly higher in the pazopanib group (4.6 versus 1.6 months), and benefit was consistent across all histologic subtypes. There was no significant difference in overall survival (12.5 versus 10.7 months, hazard ratio 0.86, 95% CI0.67-1.1) [113]. The best overall response was partial response in 6 versus 0% of the pazopanib and placebo groups, respectively, and stable disease in 67 versus 38%. Based upon these data, in April 2012, pazopanib was approved for treatment of patients with advanced STS (but not for adipocytic or GIST) who have received prior chemotherapy by FDA.

Bevacizumab: Bevacizumab is a monoclonal antibody targeting VEGF. The combination of bevacizumab plus doxorubicin showed some modest activity in 17 anthracycline-naive patients with metastatic STS [114]. Although there were only two partial responses, 11 had stable disease for 12 weeks or more, depicting some activity of this combination.

Sorafenib: Sorafenib, a tyrosine kinase activity has also been evaluated in STS. In a phase II trial of 120 patients with six different histologic types of STS who received sorafenib 400 mg twice daily, there was one objective partial response among 37 leiomyosarcomas, one complete and four partial responses among 37 angiosarcomas (14%), and no objective responses in MPNST, malignant fibrous histiocytoma, synovial sarcoma, or other histotypes [115].

Crizotinib: Crizotinib is an orally ATP-competitive inhibitor of the ALK and MET tyrosine kinases. It has shown antitumor activity in ALK-rearranged inflammatory myofibroblastic tumor [116].

Regorafenib: Regorafinib is a multikinase inhibitor, which has 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 doxorubicin, ifosfamide, trabectedin, or pazopanib (median of prior lines 2, range 1-3). The median PFS ofleimyosarcoma 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 [117].

Cediranib: Cediranib is a potent oral inhibitor of all three VEGFRs. Its activity in alveolar soft part sarcoma was elucidated in a phase II

trial of 46 patients with unrespectable disease [118]. The objective response rate was 35%, and 60% had stable disease; the six-month disease control rate was 84%.

Olartumumab: Olaratumab is a human anti-PDGFR-α monoclonal antibody. PDGFR is a cell surface receptor that has ligands, which upon ligand binding, dimerize and enable intracellular signaling and for the growth of cells and interactions with the tumor microenvironment, as well as angiogenesis in normal cells as well. One randomised phase 2 study of doxorubicin plus olaratumab treatment in patients with unresectable or metastatic soft-tissue sarcoma showed encouraging results. The overall tumor response in the intention to treat population was about 18% in the combination and 12% in the doxorubicin only arm, and the difference was not statistically significant. There was a PFS advantage in the combination *vs.* the doxorubicin-only arm. There was a significant OS advantage for patients who received the combination of olaratumab plus doxorubicin *vs.* doxorubicin alone. Overall, the survival benefits seemed to be in all subgroups including in tumors such as leiomyosarcoma [119].

Ridaforolimus: Ridaforolimus is an mTOR inhibitor, which has been tested in a phase II trial in advanced STS. Out of 212 patients in this study, 28.8% showed clinical benefit [119]. 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 versus 14.7 weeks for placebo; HR=0.72; P=0.001). However, this trial did not show any benefit in OS.

Vorinostat: Vorinostat is a HDAC inhibitor, which has been tested in heavily pretreated metastatic STS. In a recent Multicentric phase II trial, 40 Soft Tissue Sarcoma patients were treated with vorinostat. Best response after three cycles of treatment was stable disease (n=9, 23%). Median progression-free survival and overall survival were 3.2 and 12.3 months, respectively. Six patients showed long-lasting disease stabilization for up to ten cycles. Despite this low response in this trial, it does call for further exploratory studies using this agent to find out biomarkers for its activity.

Evolving Genomic Techniques: Genomic characterization of cancer through next generation sequencing (NGS) techniques are transforming our understanding of solid tumors and has been deployed in the clinical setting to quickly genotype several to hundreds of genes in a rapid fashion. Recently, both The Cancer Genome Atlas (TCGA) of the National Institutes of Health (NIH) and the European efforts toward the International Cancer Genome Consortium have allocated resources to study multiple specific sarcoma types. It is hoped that these efforts will provide a catalog of mutations or other genomic disturbances relevant to sarcomas that will provide other potential avenues for application of targeted and rational therapies.

Perspective

As our understanding of the mechanisms of tumorgenesis and the pathways required for sarcoma survival and metastasis increases, it is hoped that we can tailor our therapy to the presence of functional genes: molecular profiling will become much more used in the near future and more such targeted compounds may become reality. However, much work is of course still needed to unfold the complex personalized networks of tumor proliferation and resistance mechanisms to better achieve the goal of truly personalized treatment for sarcoma. Currently, there is some optimism that newer generations of agents might prove effective in them.

Conclusion

Despite recent improvements in therapeutic management of sarcoma, ongoing challenges in improving the response to therapy warrants new approaches in terms of both agents and modes of delivery, to improve overall patient survival. Recent years have witnessed the phenomenal strides made in the treatment of sarcoma driven by specific pathways; it suggest that [Paul] Ehrlich's magic bullet has at last been realized in the field of oncology. This is targeted (intelligent) delivery of therapy, with much better tolerance providing means to deliver therapy for longer periods with resultant better disease control: greater efficacy, less toxicity. The therapeutic window for this heterogeneous and difficult to manage group of malignancies have been opened wider than ever before.

Unless spectacular new therapeutic opportunities arise-and, despite all research efforts, these do not seem to wait around the corner-optimization of therapies with incorporating targeted therapy will have to be addressed in a big manner!

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