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Review Article

The evolving role of precision medicine in the management of advanced sarcomas – A mini review

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ABSTRACT

Sarcomas are a heterogenous group of cancers, traditionally with dismal outcomes. They were initially treated with histology agnostic chemotherapy-based regimens usually centered around anthracyclines. With the availability of molecular diagnostics especially next-generation sequencing, the advanced genomics of sarcomas was slowly unveiled. Precision medicine not only enables a better diagnosis in sarcomas but also allows in identifying better targets for treatment of sarcoma subtypes. GENSARC study proved that using correct molecular diagnostics, enabled in a better diagnosis and treatment of soft tissue sarcomas (STSs). Notable examples of targeted therapies with great success in sarcomas include imatinib and other tyrosine kinase inhibitors in gastrointestinal stromal tumors, neurotrophic tyrosine receptor kinase inhibitors infantile fibrosarcoma, and crizotinib in inflammatory myofibroblastic tumors. Thus, treatment of sarcomas has been gradually changing from traditional chemotherapy-based treatments to the modern targeted therapy. In this review, we hope to impress on the evolving role of precision medicine in sarcoma subtypes especially STS.

Keywords: Sarcoma, Precision medicine, Targeted therapy, Molecular diagnostics

INTRODUCTION

Sarcomas are an extremely heterogenous group, with more than 80 histologic subtypes already known and more being added each year.[1] Surgery remains the cornerstone of cure in localized disease, supplemented with adjuvant radiotherapy and/or chemotherapy. However, in advanced/metastatic disease, systemic therapy is usually the only option, often with dismal outcomes. Up to the turn of the century, the management of advanced soft-tissue sarcomas (STS) was dominated by a "one size fits all approach," without any consideration for the pathological intricacies of individual subtypes. Doxorubicin, ifosfamide, gemcitabine, or dacarbazine constituted the common chemotherapeutic options. This has thankfully been replaced by a more tailored approach, with trials and treatment aimed at specific histologies and tissue-agnostic molecular targets.[2] In this review, we hope to succinctly elucidate on a few points regarding precision therapy in sarcomas.

MOLECULAR SUB-CLASSIFICATION OF SARCOMAS

Beginning with the discovery of the t(11;22) (q24;q12) translocation in Ewing's sarcoma (ES),[3] technological advances have permitted the identification of several recurrent chromosomal abnormalities and mutations in several sarcoma subtypes. So much so, more than 45% of all

sarcomas have been described to have recurrent cytogenetic/molecular abnormalities in the most recent WHO Classification of Tumors of Soft Tissue and Bone.[1]

Broadly, sarcomas are now divided into two categories based on genetic abnormalities:[4] Translocation-related sarcomas – that have normal karyotypes and a dominant cytogenetic abnormality (such as a translocation or deletion of a tumor suppressor gene), and a group of tumors that have complex karyotypes and multiple cytogenetic abnormalities. Translocation-related sarcomas are relatively more common and account for around 26% of all sarcoma subtypes listed in the WHO classification.[1,5] Most such translocations encode for abnormal transcription factors that deregulate normal cell metabolism. Examples of such tumors include ES, synovial sarcoma (SS), and alveolar rhabdomyosarcoma. Less commonly, deranged signaling may be caused by chimeric tyrosine kinases (such as in inflammatory myofibroblastic tumor [IMFT] and infantile fibrosarcoma) or chimeric autocrine growth factors (such as in certain cases of tenosynovial giant cell tumor [TGCT] and dermatofibrosarcoma protuberans [DFSP]).[6]

MOLECULAR PROFILING AND ITS METHODOLOGY

Molecular profiling refers to the assessment of the genetic makeup of sarcoma cells from a biopsy specimen. Such profiling may be accomplished using DNA, RNA, or even proteins. Physician education in this regard is vital as deciding on the necessity, timing, and selection of appropriate tests to order can be perplexing. Even the interpretation of test results and their correct utilization in informed therapy-related decision-making requires practice. The following is a brief summary of the techniques used to detect genomic imbalances in sarcomas.[6,7]

Conventional cytogenetic analysis

Conventional karyotyping is now only of historical importance in sarcoma management. Its disadvantages include a long turnaround time (TAT), the requirement of a cell culture medium for processing, low resolution, limited utility, and its inability to pick up cryptic mutations. These drawbacks have led to this tool being obsolete.

Fluorescent *in situ* hybridization (FISH)

This technique uses labeled complementary DNA, RNA, or modified nucleic acid strand probes to localize a gene of interest in a tumor sample. Different probes are used for FISH testing in STS, break-apart and dual-fusion probes are used for sarcomas with translocation. Locus specific probes are used to identify insertions and deletions. Some of the commonly used break apart probes clinically include

a. SS18 break apart probe in SS
b. MDM2 probe in well-differentiated liposarcoma/atypical lipomatous tumors (ALT/WDS), dedifferentiated liposarcoma, parosteal sarcoma, and malignant peripheral nerve sheath tumor (MPNST)
c. FUS/DDIT3 break apart probes in myxoid/round cell liposarcoma (MLPS)
d. ALK in IMFT and PDGB in DFSP, respectively.

Indication of dual fusion probes includes detection of EWSR1 and WT1 in ES, desmoplastic small round cell tumor (DSCRT)

FISH excels over karyotyping in that there is no culture required and the testing can be done on formalin-fixed tissue as well. It is also faster and can be done on minute tissue samples. Both FISH and polymerase chain reaction (PCR) have a capacity for high resolution (150–200 kb), with an ability to pick up even cryptic translocations. The advantages over PCR are in assessment of tissue with a mixed cell population, wherein only a specific subset of tumor cells might harbor the target gene translocation. Furthermore, in a given translocation with a common break point, but involving multiple fusion partners (such as in ES), FISH can diagnose all known rearrangements whereas PCR would require multiple primers to cover all possible fusion partners. The disadvantages of FISH are its low specificity and its ability to detect only known genetic abnormalities.

PCR

This technique uses specific primers to amplify known DNA or RNA sequences. Added to its greater sensitivity and high resolution, it also has a conveniently short TAT. Its disadvantages include its greater expense, lack of wide availability, and an inability to diagnose cryptic mutations. With both FISH and PCR, care should be taken while interpreting borderline values, and in such unequivocal cases, the reports from one modality should be confirmed with the other.

Massive parallel sequencing (MPS)

MPS uses a comprehensive whole exome/genome/transcriptome approach to diagnose mutations at the nucleotide level. For instance, they can identify novel mutations such as *BCOR–CCNB3* in undifferentiated small-cell sarcoma,[8] CNVs, and point mutations. Sequencing techniques include the traditional Sanger method, which takes 1–2 weeks for results, and next-generation sequencing (NGS), which is a more rapid, high throughput technique, but requires trained staff for the operation and interpretation of data. Sequencing is more useful than PCR or FISH for the diagnosis of unknown mutations. While both fresh and fixed tissues can be used, adequate genetic material (DNA or

RNA) is needed for proper interpretation. NGS sequencing includes the following approaches.[9]

Whole genome sequencing (WGS)

Most comprehensive sequencing technique, but is clinically not practical as it is cumbersome to perform and analyze the large amount of data created, not cost effective, the functional significance of most of the variants detected by WGS is not known; hence, it is still considered as experimental.

Targeted sequencing (whole exome sequencing [WES] or cancer gene panels)

Commercially available gene panels sequence for a limited number of genes 100–300 and hence limit the general cost of sequencing, but the disadvantage being it might miss on the novel gene mutations in most of the cases. Exome accounts for about 2% of the entire genome. Therefore, WES has the obvious advantage of screening the entire exome and being easier and faster to perform, interpret and being more cost effective with screening of clinically relevant mutations. Some examples of application of WES include *NAB–STAT6* in solitary fibrous tumor (SFT).[10] It can also detect point mutations and *insertions and deletions* (indels) *such* as *KIT/PDGFRA* and *SDHA/B* in gastrointestinal stromal tumors (GIST), CTNNB1 in desmoid tumors, *IDH1* or *IDH2* in enchondroma/chondrosarcoma, and *NF1* in MPNST. Because most of the large gene deletions and structural translocations occur at various sites of introns, WEScan miss them for instance in BRCA1 and BRCA 2 can be missed out on WES.

RNA sequencing (transcriptome sequencing)

The attractive part of transcriptome sequencing in STS is in its applicability to detect structural rearrangements, large genomic deletions which are missed out by WES. They, hence, also detect novel fusion genes. Some of the clinical break through achieved by RNA sequencing includes, *WHAE-NUTM2A/B* in high-grade endometrial stromal sarcoma (ESS), *WWTR1-CAMTA1* in epithelioid hemangioendothelioma, and *BCOR-CCNB3* in undifferentiated round cell sarcoma. However, RNA sequencing is still not used wide spread as it is more technically challenging to be performed as they require high quality RNA.

MOLECULAR TESTING IN SARCOMAS

Molecular testing now plays a pivotal role in the diagnosis, classification, and treatment of sarcomas. STS can be diagnosed by light microscopy and immunohistochemistry (IHC), but in late presentations with metastatic disease, they tend to become less differentiated and traditional methods of diagnosis tend to falter. Histological diagnosis in sarcomas is often difficult, even more so in low-volume centers. Even an expert sarcoma pathologist cannot reliably diagnose all the sarcoma subtypes based on the traditional diagnostic methods alone. Proof of concept of the same fact was obtained from the GENSARC trial, a prospective observational study which examined the role of molecular diagnostics in improving sarcoma diagnosis compared to an expert sarcoma pathologist.[11] In the final analysis, of 395 patients with six subtypes of sarcoma, there was a change in diagnosis in 53 (13.8%) patients, and a resultant change in primary management or prognosis in 45 (11.7%) patients. This study conclusively proved the importance of molecular diagnostics in sarcoma. As with all tools, however, molecular tests are best used in conjunction with clinical and histopathological data, rather than in isolation.

APPLICATION OF PRECISION MEDICINE IN DIAGNOSING STS

Listed below are some selected situations exemplifying how precision medicine aids in the diagnosis of sarcoma.

Small round cell tumors

Small blue round cell tumors (SBRCT) may be mesenchymal, epithelial or lymphoreticular in origin. They are often difficult to differentiate by light microscopy or IHC alone. Sarcomas presenting with small round cell phenotype include ES, RMS, poorly differentiated SS, DSCRT, and MLPS. As an illustrative example, poorly differentiated SS is often confused with extra skeletal ES. Although they can share a few clinical and histological similarities, they can be differentiated molecularly based on the presence or absence of *SS18–SSX* fusions or *SS18–* rearrangement which is specific for SS.[12] Similarly, there is a subset of SBRCT which behaves clinically similar to ES (Ewing like) but, unlike ES, have distinct rearrangements between EWSR1 and non-ETS partner genes such as *PATZ1*, *POU5F1*, and *SMARCA5*. Some of these tumors behave aggressively.[13] A special mention of two subtype of undifferentiated SBRCT is necessary, the first of them being *CIC-DUX4* gene fusion associated sarcomas, it is the most common mutation found in EWSR1-negative SBRCTs. It, usually, occurs in the young adults between third to fourth decades of life and commonly affects the soft tissue rather than bone. It is associated with a more aggressive course and poor outcomes.[14] *BCOR-CCNB3* fusions associated round cell sarcoma are another subset of sarcomas, usually seen in adolescent and young males, commonly affecting the long bones and has relatively better prognosis.[8]

Spindle cell tumors

Sarcomas presenting with spindle cell morphology include, fibrosarcoma, leiomyosarcoma, MPNST, and

monophasic SS. Infantile fibrosarcoma is often confused morphologically with other spindle cell tumors, such as the adult-form of fibrosarcoma, infantile fibromatosis, and infantile myofibromatosis. Molecular testing for the *ETV6*–Neurotrophic tyrosine receptor kinase (*NTRK3*) fusion gene, specific for infantile fibrosarcoma,[15] and enables us to confirm the diagnosis in perplexing cases. Molecular testing for *NTRK* in such tumors has therapeutic implications. On the same note, monophasic SS presenting in the pleural cavity can be differentiated molecularly from SFT, sarcomatoid malignant mesothelioma, and MPNST based on the presence of *SS18-SSX* gene fusion.

1. Differentiating between a lipoma and an ALT/WDS is important as both of them have contrasting management principles. Dedifferentiated liposarcoma with high grades of dedifferentiation often cannot be differentiated from other high grade pleomorphic sarcoma or poorly differentiated sarcoma by histology alone, but the molecular demonstration of *MDM2* (+*CDK4*) amplification in ALT/WDS or dedifferentiated LPS enables us to clinch the diagnosis[16]
2. Clear cell sarcoma (CCS), often confused with melanoma, can be recognized by testing for t(12;22)(q13;q12) translocation and its associated *EWSR1–ATF1* fusion gene, which are associated with CCS.[17]

Table 1 summarizes the important molecular changes with appropriate tests for diagnosis of commonly encountered sarcomas.[41,43,44,52,53]

ROLE OF MOLECULAR DIAGNOSTICS IN THERAPY

For metastatic soft tissue tumors, anthracycline-based chemotherapy is the usual first line,[18] with a median OS of 8–17 months and an overall response rate (ORR) of 10–30%. [2,19] Addition of other agents to an anthracycline bone can increase the PFS, but has no beneficial effects on the OS. Most STS inevitably progress after a period of response to anthracyclines. Other chemotherapeutic options, too, such as gemcitabine, ifosfamide, and dacarbazine, have limited efficacy.[20] Later on, it was realized that several sarcoma histological subtypes behave differently with regard to their response to chemotherapy. For example, MLPS responds to a combination of doxorubicin and ifosfamide whereas CCS does not respond to the same treatment.[21] Similarly, Trabectedin was found to increase PFS in L-sarcomas and eribulin in liposarcomas. Fortunately, over the years, we have gained a better understanding of the oncogenic pathways involved in the development of sarcomatous tumors. Precision medicine has also employed genomic and somatic biomarkers in predicting response to treatment. Illustrating this fact is the observation that trabectedin showed better clinical response in BRCA 1 mutated patients with advanced STS.

One of the most important applicability of molecular sequencing in sarcomas is also identify a targetable mutation. However, it is also equally important to remember that not all targeted mutations have an appropriate treatment as of yet and most of these treatments are still not clinically relevant. The management of advanced sarcomas is also gradually moving away from a histology-centric approach to a target-based, histology-agnostic approach. Lucchesi *et al*.[22] analyzed 584 patients with advanced STS and identified that using an NGS-based database, 41% of patients had a potential targetable mutation. Similarly, Boddu *et al*.,[23] in their single center study of 114 patients with sarcoma, discovered that 49% patients had a mutation which could be targeted, of which 15 patients were treated with targeted drugs, and 26% of these patients benefitted clinically. Thus, molecular diagnostics have ushered in an era of precision medicine in sarcoma management, as illustrated below.

Table 2 gives a summary of important clinical trials using targeted therapy in STS.

GISTs

GIST is a prime example, where targeted therapy revolutionized management. Prior 1998 there was no effective therapy for advanced GIST. Discovery of KIT and PFGFRA changed the paradigm of treatment in GIST**.** Over 80% of GISTs have mutations in the KIT and PDGFRA genes, making them responsive to Imatinib, with a response rate of 69% and a PFS of up to 26 months.[46] The particulars of these mutations, however, give us even more insight into their sensitivity to Imatinib. Patients with mutations in exons 4 or 12 of PDGFRA respond to imatinib, whereas exon 18 D842v mutations are imatinib-refractory.[24] On progression to imatinib, several targeted options are available, including sunitinib, regorafenib, avapritinib, and ripretinib.[47-50] Wild-type GISTs, which lack cKIT and PDGFRA mutations, are mostly SDH-deficient and exhibit O6-methylguanine-DNA methyltransferase promoter methylation, but trials of alkylating agents in this subtype have failed to show any benefit.[25] In wild-type GISTs that are SDH-competent, vandetanib (an inhibitor of VEGFR2, RET, and EGFT) has been tried in V600E-mutated cases with good results.[26]

PEComas

PEComas are a group of related tumors that include angiomyolipoma of the kidney, clear cell sugar tumor of the lung, and lymphangioleiomyomatosis. These tumors are characterized by the presence of TSC1 and TSC2 mutations affecting the mammalian target of rapamycin (mTOR) pathway. mTOR inhibitors, such as sirolimus and temsirolimus, have been used in PEComas with good clinical responses in case reports.[27]

Table 1: Summary of genetic events occurring in clinically relevant sarcomas with testing recommendations.

Ref	Tumor subtype	Translocations and others	Fusion gene (s) or other	Indication and choice of testing
	Adipocytic tumors			
	Lipoma	12q15 rearrangements, loss of 13 q material	*HMGA2 HMGA2-LPP HMGA1↓ C13orf1* expression	It is a clinical diagnosis; routine genetic testing is not advised
[11]	ALT/WDS/ Dedifferentiated liposarcoma	Supernumerary ring or giant rod chromosome (s) amplification of 12q14-15	*MDM2* amplification ± *CDK4* amplification and *DUSP12* amplification in some cases with 1q21-25 amplicon	MDM2 amplification by IHC/FISH/PCR testing is recommended in unequivocal cases. To differentiate from benign lipoma/poorly differentiated sarcoma
(11)	Myxoid/round cell liposarcoma	t (12;16)(q13;p11) t (12;22) (q13;q12)	*FUS-DDIT3 EWSR1-DDIT3*	Testing by FISH or PCR is recommended for all patients. To differentiate from other retroperitoneal sarcoma if located in retroperitoneum
	Fibroblastic/myofibroblastic tumors			
[41]	Desmoid-type fibromatosis	+8, +205q21-22 loss	Unknown *APC* inactivating mutations (germline; may be seen) Sporadic lesion show CTNNB1 mutations	Somatic CTNNB1 testing is recommended in all cases by IHC, PCR or sequencing. If negative to consider for APC testing
[11]	DFSP	t (17;22)(q21.3;q13) or r (17;22)	*COL1A1-PDGFB*	Testing by FISH or PCR is recommended for all patient as it predicts sensitivity to TKI
[6]	Extra-pleural SFT	12q13 rearrangements	*NAB2-STAT6*	Rare tumor, testing is advisable for all cases, IHC for STAT6 or sequencing to demonstrate mutation is necessary
[40,42]	IMFT	t (1;2)(q22;p23) t (2;19) (p23;p13) t (2;17)(p23;q23)	*TPM3-ALK TPM4-ALK CLTC-ALK*	Testing for ALK and ROS1 translocation by FISH, PCR is recommended as it predicts response to Crizotinib (for ALK testing IHC can be a good indicator). If ROS1 and ALK negative test for *NTRK* fusion
[40]	Congenital/infantile fibrosarcoma	t (12;15)(p13;q25)	*ETV6-NTRK3*	Testing of IHC for *NTRK* as a screening test followed by PCR or Sequencing for confirmation is recommended in all cases
	Skeletal muscle tumors			
(6)	ERMS	Loss or UPD of 11p15.5+2, +8, +11, +12, +13, +20	*IGF2, H19, CDKN1C* and *HOTS*	Routine testing is not recommended
(6)	Alveolar rhabdomyosarcoma	t (2;13)(q35;q14) t (1;13) (p36;q14) t (X; 2)(q13;q35) t (2;2)(q35;p23)	*PAX3-FOXO1 PAX7-FOXO1 PAX3-FOXO4 PAX3-NCOA1*	Testing of translocation by FISH is important for diagnostic and prognostic implications
(6)	Spindle cell RMS	8q13 rearrangements	*SRF-NCOA2 TEAD1-NCOA2*	Routine testing not recommended
	Chondro-osseous tumors			
[43]	Mesenchymal chondrosarcoma	inv (8)(q13;q21)	*HEY1-NCOA2*	Rare tumor, moderately chemosensitive unlike conventional chondrosarcoma, testing by FISH if diagnosis is unequivocal
[43]	Conventional Chondrosarcoma		IDH1 and IDH2	Testing is recommended as it has diagnostic and therapeutic implications (could be useful to differentiate between osteosarcoma)

(Contd...)

Table 1: *(Continued)*

Ref	Tumor subtype	Translocations and others	Fusion gene (s) or other	Indication and choice of testing
	Nerve sheath tumors			
[6]	MPNST	17q loss 9p loss	*NF1* (germline and somatic) *CDKN2A*	Routine testing for NF1 is not generally recommended
	Others			
[44]	Low grade ESS	t (7;17) (p15;q21) t (7;17) (p15;q21)	JAZF1–SUZ12, JAZF1–PHF1	Testing by FISH or MPS is recommended in unequivocal cases
[44]	High grade ESS	t (10;17) (q22-23;p13)	YWHAE–NUTM2A and/or NUTM2B, BCOR and SMARCA1	Testing is recommended
	Tumors of uncertain differentiation			
[6]	Synovial sarcoma	t (X; 18) (p11.2; q11.2)	*SS18-SSX1 SS18-SSX2*	Testing for SS18 translocation by FISH and PCR is recommended in all cases as it differentiates from poorly differentiated ES
[31]	Epithelioid sarcoma	22q11.2 anomalies+8q, often as i (8)(q10)	*SMARCB1*	Testing for loss of INI by IHC is recommended as they have therapeutic implication
[45]	Alveolar soft part sarcoma	del (17) t (X; 17) (p11;q25)	*ASPSCR1-TFE3*	IHC for TFE3, FISH for the characteristic translocation is recommended in most of the cases
[17]	CCS	t (12;22)(q13;q12)	*EWSR1-ATF1*	Chemo resistant tumor. FISH for specific translocation is recommended in all cases as they mimic melanoma clinically
[43]	Extra-skeletal myxoid chondrosarcoma	t (9;22)(q22;q12) t (9;17) (q22;q11)	*EWSR1-NR4A3* *TAF15-NR4A3*	
[11]	Ewing sarcoma	t (11;22)(q24;q12) t (21;22) (q22;q12)	*EWSR1-FLI1 EWSR1-ERG*	Currently *EWSR1* testing is recommended in all cases
[8,14]	Undifferentiated round cell sarcoma	t(4;19)(q35;q13) t (10;19) (q26;13) inv X (p11.4p 11.22)	*CIC-DUX4* *BCOR-CCNB3*	FISH or MPS for CIC-DUX4 and IHC or FISH for BCOR CCNB3 is recommended
[17]	Desmoplastic small round cell tumor	t (11;22)(p13;q12)	*EWSR1-WT1*	IHC for WT1 or FISH for mutation to be considered in all cases as it is a rare aggressive tumor
[27]	Perivascular Epithelioid Cell Neoplasms PEComa	Deletion or loss of 16p	*TSC1, TSC2*	NGS for TSC1 and TSC2 testing is recommended in all cases as they predict sensitivity to mTOR inhibitors
[24]	GIST		c-KIT, exon 11,13,17,19 PDGFRA exon 12,14,18	c-kit and PDGFRA mutation testing by PCR, FISH is recommended in all cases. If negative testing for SDH B IHC and BRAF, NF1 testing by PCR or sequencing to be done to rule out Wild type GIST

DFSP

DFSP is a locally aggressive tumor most commonly seen on the trunk followed by proximal extremities. Fibrosarcomatous areas occasionally occur in DFSP, which are associated with increased chance of metastasis and P53 mutations.[28] It is characterized by a t(17;22) translocation involving *COL1A1* and *PDGFB* genes. The consequent hyperactivation of PDGFRB rendering them sensitive to targeted therapy with the tyrosine kinase inhibitors (TKI) imatinib.[29]

Alveolar soft part sarcoma

It is a rare, slow-growing tumor with propensity to metastasize to the brain and lungs.[45] It is chemoresistant, but responds to TKIs such as sunitinib and pazopanib. As MET is also overexpressed

Table 2: Summary of clinically relevant trials using targeted treatment in STS.

Study	Histology	Target	Drug	ORR	Study design	PFS (months)
[46]	GIST	KIT and/or	Imatinib	51%	Phase III	20.4
[47]		PDGFR	Sunitinib	33%	Phase III	6.0 v 1.4
[48]			Regorafenib	4.5%	Phase III	4.8 v 0.9
[49,50]			Avapritinib	86% (PDGFRD842V)	Phase I	mDOR – NR
			ripretinib	9.4%	Phase III	6.3 v 1
[29]	DFSP	PDGFR	Imatinib	46–70%	Phase II	Median TTP 1.7 years
[34,35]	TGCT	CSF1R	Imatinib	19%	Retrospective	21.0
			Pexidartinib	39%	Phase III	NR
[32]	IMFT	ALK and/or ROS1	Crizotinib	50% (ALK positive) 14% (ALKnegative)	Phase II	2-year PFS 49% (ALK positive) 2-year PFS 36% (ALK negative)
[30,51]	ASPS	VEGFR	Pazopanib	27%	Retrospective	13.6
		MET	Cediranib Sunitinib Tivatinib, Cabozantinib And crizotinib	35%	Phase II	NR
[30,36]	CCS	MET	Tivatinib	2%	Phase II	1.9
			Crizotinib	3.8%		135 days
[40]	Infantile fibrosarcoma and other TRK fusion associated sarcomas	*NTRK*	Entrectinib	46%	Phase I/II basket trials	11.0
			Larotrectinib	87%		28.3
[27]	PEcoma	mTOR	Sirolimus Temsirolimus	7/10	Retrospective	mOS=2.4 years
[52]	LPS	MDM2 CDK 4/6	(MG7112) Palbociclib	5% NR	Phase II	17.9 weeks
[31]	ES	EZH2	Tazemetostat	18%	Phase II (basket trial)	5.5
[53]	LG-ESS	ER, PR	Aromatase inhibitors	46%	Retrospective	36.0
[33]	Plexiform neurofibroma	MEK 1 &2	Selumetinib	68%	Phase II	NR

in these tumors, MET inhibitors, such as tivatinib, have also been found to be useful in their management.[30,51]

Epithelioid sarcoma

ES is a rare aggressive malignancy, with dismal outcomes in advanced stage. About 90% of these tumors are characterized by INI/SMARCB1 deficiency which leads to elevated levels of enhancer of Zeste homolog 2 (EZH2) and finally promotes oncogenesis. Tazemetostat is an EZH2 inhibitor with Phase II basket trials demonstrating good activity of the drug.[31]

IMFT

It is a tumor with intermediate malignant potential.[42] It can occur anywhere but is most commonly seen in lungs, GIT, and retroperitoneum. The hallmark of this tumor is the coexistence of myofibroblastic tissue with immune-cell infiltrates. ALK fusion rearrangements, identified by FISH, are seen in about half of such tumors, more commonly in children. This is clinically targeted by the ALK inhibitor crizotinib.[32] ALK fusion negative patients are to be tested for ROS 1 and *NTRK* as they are targetable mutations.

NF1-related plexiform neurofibroma

Plexiform neurofibromas are seen in 20–50% patients with NF1. They can lead to disfigurement, pain and high risk of transformation to MPNST. These tumors are dependent on MEK1 and 2 signaling for survival. Selumetinib, a MAP kinase inhibitor has shown clinical benefit in children treated with this drug.[33]

TGCT

It is an aggressive tumor of the synovial tissue, usually affecting wrists. These tumors are characterized by pathognomonic gene fusions involving colony stimulating factor-1 (CSF-1). This has been clinically targeted by imatinib and nilotinib with modest responses.[34] Pexidartinib is potent CSF-1 R inhibitor. Phase III trial (ENLIVEN) showed good results for the drug leading to its FDA approval and hence supporting the role of targeted therapies in these rare tumors.[35]

CCS

CCS is a rare chemo sensitive and radiosensitive tumor. Its survival is dependent on MET signaling, tivatinib has been explored in the same setting and has failed to achieve to show clinical response.[30] Crizotinib another MET inhibitor has also been tried and failed.[36]

Angiosarcoma

This is a rare aggressive malignancy which is chemosensitive but outcomes are poor because it is locally aggressive and has metastatic potential. As the name indicates, they are characterized by increased expression of vascular endothelial growth factor (VEGF), which is explored clinically using anti VEGF agents such as pazopanib, sorafenib, and bevacizumab.[37] Retrospective studies have also shown efficacy of propranolol, a non-selective beta blocker in treatment of angiosarcoma.[38] Combination of propranolol, methotrexate, and vinblastine as metronomic therapy has shown 100% efficacy in one trial.[39]

Role of TRK in advanced STS

NTRK gene fusions as tissue-agnostic oncogenic drivers are seen in subtypes of STS. This has been explored for targeted therapies in form of TRK inhibitors. Tumors with high *NTRK* gene fusion among STS include infantile fibrosarcoma and ALK, ROS 1 negative IMFT. Larotrectinib is the first in class TRK inhibitor, ORR was 87% in the STS subgroup with 71 patients bearing *NTRK* mutations. *NTRK* testing with therapy has shown great leaps in management of advanced STSs like infantile Fibrosarcoma and GIST.[40]

CONCLUSION

Soon we are progressing into era of precision medicine as highlighted by the approval of drugs such as tazemetostat and avapritinib. We have progressed from the traditional histology agnostic therapy to more recent targeted therapy. Management of STS is being increasing dependent on molecular diagnostics that enable better characterization, diagnosis, and therapeutic-targeting of tumors. With newer targeted therapies also being discovered, there is much promise for a brighter future in the management of advanced sarcomas.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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