Molecular targeted therapies in non-GIST soft tissue sarcomas: what the radiologist needs to know

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Abstract

Non-gastrointestinal stromal soft tissue sarcomas are uncommon neoplasms that have a dismal prognosis due to a high incidence of metastases and a poor response to conventional chemotherapy. The identification of characteristic genetic alterations in several of these tumors has opened the window for molecular targeted therapies in patients who have failed conventional chemotherapy. Imaging plays a critical role in assessing the response to these novel therapeutic agents. Just like the response of gastrointestinal stromal tumors to imatinib, the response of non-gastrointestinal stromal soft tissue sarcomas to molecular targeted drugs is better evaluated on imaging by alternate tumor response criteria such as the Choi criteria. In addition, these drugs are associated with distinct class-specific drug toxicities that can come to attention for the first time on imaging. The purpose of this article is to provide a primer for the radiologist on the various molecular targeted therapies in advanced/metastatic non-gastrointestinal stromal soft tissue sarcomas with emphasis on the role of imaging in assessing treatment response and complications.

Keywords: Soft tissue sarcomas; molecular targeted therapies; CT; MRI; PET/CT; drug toxicities.

Introduction

In 2002, imatinib mesylate (Gleevec), a c-KIT tyrosine kinase inhibitor (TKI), which was initially used to treat chronic myeloid leukemia, was granted accelerated US Food and Drug Administration (FDA) approval for the treatment of advanced or metastatic gastrointestinal stromal tumor (GIST). Sunitinib, a vascular endothelial growth factor receptor (VEGFR) inhibitor, approved for use in metastatic renal cell carcinoma, was the next drug found to have a beneficial effect in imatinib-resistant GISTs. Understanding the molecular pathways of GISTs and the identification of potential new molecular targets led to a quest to replicate the success of imatinib in non-GIST soft tissue sarcomas (STS). More than a decade later, the usefulness of several new TKIs that are close congeners of imatinib is being explored in the treatment of advanced and metastatic STS. As more of these drugs are being developed and approved by the FDA, there is a greater need for radiologists to be aware of the molecular pathways involved in sarcomagenesis, treatment response patterns and frequently encountered toxicities.

STSs are uncommon tumors of mesenchymal origin; they account for about 1% of all malignancies[1]. They arise from connective tissue virtually anywhere in the body, but most commonly in the extremities and the retroperitoneum. Several histologic subtypes of sarcomas exist (more than 50) of which the common types in adults are liposarcoma (LPS), leiomyosarcoma (LMS), GIST, and synovial sarcoma (SS)[2]. STSs are clinically challenging to manage. More than 50% of patients have metastatic disease at presentation, frequently in the lungs and liver[3]. Considerable progress has been made in the treatment of GISTs with the advent of imatinib and its congeners. However, the management of most non-GIST STSs has not met with similar success. Surgery with wide resection margins with or without radiotherapy is the standard of care for the primary non-GIST STSs[2,4].
Summary of molecular targeted drugs used in non-GIST STS, their targets and class-specific drug toxicities

| Molecular targeted drug | Mechanism of action | Soft tissue sarcoma | Class-specific drug toxicities |
|-------------------------|---------------------|---------------------|-------------------------------|
| Imatinib mesylate        | Inhibits ABL, c-KIT, PDGF, CSF1 | Aggressive fibromatosis, dermatofibrosarcoma protuberans, pigmented villonodular synovitis | Fluid retention |
| Tyrosine kinase inhibitors and antibodies (non-imatinib) | Inhibit VEGF, PDGF, Src kinases | Leiomyosarcoma, solitary fibrous tumor, synovial sarcoma | Hepatobiliary, pancreatic and bowel-related complications, thromboembolic phenomena, pleural effusions (dasatinib) |
| mTOR inhibitors          | Inhibit the PI3K-AKT-mTOR pathway | PEComa | Non-infectious pneumonitis, acute cholecystitis |
| Trabectedin              | Unknown (probably inactivates FUS-CHOP oncogene) | Myxoid liposarcoma, leiomyosarcoma | Capillary leak syndrome |

GIST, gastrointestinal stromal tumor; STS, soft tissue sarcoma; VEGF, vascular endothelial growth factor; PDGF, platelet-derived growth factor; CSF1, colony-stimulating factor 1.

Cancer pathways of non-GIST STSs and potential targets for therapies

STSs are broadly classified at a molecular level into those with simple diploid karyotypes consisting of specific predictable molecular aberrations and those with complex karyotypes consisting of non-specific genetic alterations, which are random and unpredictable[16]. STSs with complex karyotypes are associated with a high frequency of chromosomal instability, p53 and retinoblastoma pathway mutations. On the other hand, STSs with simple karyotypes are associated with specific genetic alterations such as translocations, deletions, gene amplifications and mutations[12,17]. Reciprocal translocations result in the formation of chimeric fusion proteins that affect the intracellular signal cascades. Examples of fused genes resulting from translocations in STS include the FUS-CHOP [t(12; 16)(q13; q11)] seen in 95% of cases of myxoid LPS, EWS-FL11 [t(11; 22)(q24; q12)] seen in 85% of cases of Ewing sarcoma and ASPSCR1-TFE3 [t(X; 17)(p11; q25)] seen in 99% of cases of alveolar soft part sarcoma[12,16,17]. Both simple and complex karyotypes in STS eventually cause dysregulation of several downstream signal pathways. The major pathways that play a vital role in sarcomagenesis are the VEGF pathway, the insulin-like growth factor (IGF) pathway and the mTOR pathway, each of which could potentially act as targets for several MTTs[18] (Fig. 1). The VEGF pathway plays a key role in angiogenesis mediated by several kinases including VEGF and platelet-derived growth factor (PDGF) and their receptors[18,19]. The IGF pathway is important for promoting cellular proliferation and growth and is mediated by 4 types of IGF receptors that activate intracellular signaling cascades through either the RAS-RAF-MEK-MAPK pathway or the PI3K-AKT-mTOR pathway[16]. The mTOR pathway is the final merging point for several intracellular signal cascades and can be intrinsically activated by several mutations and deletions[16].

Imatinib in non-GIST STS

Initially approved for treatment of metastatic GISTs, imatinib subsequently showed efficacy in several other STSs. Imatinib is the prototype for the class of drugs that inhibit multiple intracellular tyrosine kinases with activity against ABL, c-KIT, PDGFR, CSF1R kinases[20] (Fig. 1). The activity of imatinib in GIST is mainly due to its ability to inhibit c-KIT mediated kinases. Another tumor where imatinib acts through c-KIT-mediated kinases is aggressive fibromatosis (Fig. 2). Aggressive fibromatosis or desmoid tumor is a locally aggressive non-metastasizing mesenchymal neoplasm, which commonly presents as a firm intra-abdominal or abdominal...
Table 2  Summary of what radiologists should know about molecular targeted therapies (MTT) in advanced and metastatic non-GIST STS

| Imaging findings which indicate response to MTT | Decrease in tumor density |
|-----------------------------------------------|--------------------------|
|                                               | Decrease in enhancement  |
|                                               | – By blocking angiogenesis mediated by VEGF or PDGF pathways (TKIs) |
|                                               | – By apoptosis or hyalinization: all MTTs |
|                                               | Decrease in size         |
|                                               | Ancillary findings: hemorrhage, cystic change, transient increase in size |

| Treatment response criteria                   | Understand limitations of RECIST |

| Imaging findings indicating tumor recurrence | Increase in size |
|                                               | Increase in tumor density |
|                                               | Enhancing intratumoral nodule |

| Imaging findings of drug toxicity             | Fluid retention: anasarca, pleural effusions, pulmonary edema |
|                                               | Pneumonitis |
|                                               | Hepatic steatosis, hepatitis |
|                                               | Acute cholecystitis |
|                                               | Pancreatitis |
|                                               | Bowel-related complications: ischemic colitis, pneumatosis intestinalis |
|                                               | Arterial and venous thromboembolic phenomenon |
|                                               | Capillary leak syndrome: unilateral pulmonary edema |

MTT, molecular targeted therapy; GIST, gastrointestinal stromal tumor; STS, soft tissue sarcoma; VEGF, vascular endothelial growth factor; PDGF, platelet-derived growth factor; TKI, tyrosine kinase inhibitor; RECIST, Response Evaluation Criteria in Solid Tumors; MASS, morphology, attenuation, size and structure.

Figure 1  Cancer pathways in non-GIST STS and potential targets for therapies. VEGF/VEGFR, vascular endothelial growth factor/receptor; PDGF/PDGFR, platelet-derived growth factor/receptor; CSF1/CSF1R, colony-stimulating factor 1/receptor; IGF/IGFRm insulin-like growth factor/receptor.
wall mass in young females, often associated with familial adenomatous polyposis (FAP) syndrome. Surgical resection remains the treatment of choice for primary desmoid tumors if present in favorable locations. Non-operable and recurrent desmoids may be treated by radiotherapy or with systemic therapy with anthracyclines or hormonal therapy.

Immunohistochemistry of desmoid tumors shows strong positivity to c-KIT and PDGFB, which is the basis of successful therapy with imatinib (Fig. 2). In a study of 40 patients with unresectable or progressive fibromatosis, Penel et al. found non-progression rates of 89% and 67% for patients with previously progressive disease after 3 and 12 months of treatment, respectively.

Two other non-GIST STSs where imatinib acts through completely different targets are DFSP and PVNS. DFSP, a slow-growing mesenchymal tumor, is historically the second STS after GIST to be treated with MTT. DFSP is a locally aggressive tumor of the dermis mainly encountered in the trunk and proximal extremities of early and middle-aged men. Although a benign tumor, it has a tendency to recur locally if incompletely resected. Rarely, DFSP can have overgrowth of fibrosarcomatous components, and presents with lung metastasis in up to 4% of cases. The target for imatinib in DFSP is the PDGFB receptor, which is upregulated by the chimeric protein COL1A1-PDGFB resulting from the translocation t(17;22). This translocation is seen in excess of 90% of cases of DFSP and is the rationale behind the efficacy of imatinib. In a study of 10 patients with DFSP, McArthur et al. were able to achieve clinical response in 8 patients with locally advanced disease and partial response in 1 case of metastatic DFSP. The response in these 9 patients was attributed to the inhibition of t(17;22)-mediated activation of PDGFB.

PVNS refers to a benign neoplastic process affecting the synovium of mainly large joints such as the knee and characterized by the presence of multi-nucleated giant cells and hemosiderin deposition on histopathology. Malignant transformation in PVNS is a rare phenomenon occurring usually in the later decades of life with less than 5% incidence and seen at imaging as pulmonary and lymph nodal metastasis. At a molecular level, PVNS has a specific translocation t(1;2), which results in overexpression of the macrophage colony-stimulating factor (CSF1) gene and recruitment of cells expressing CSF1 receptor. Imatinib has been shown to have an inhibitory effect on CSF1R, independent of its activity against other kinases (Fig. 3). In a study of 29 patients with locally advanced or metastatic PVNS, Cassier et al. found objective response in 20% patients using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0.

The role of imaging in these tumors, apart from making the primary diagnosis, is to assess the response to treatment and detect drug toxicity. The assessment of response with the RECIST in these soft tissue tumors treated with MTT may have pitfalls and limitations. Similar to GIST, the response to imatinib in these tumors is better evaluated by personalized tumor response criteria involving changes in density with or without changes in size. A few studies have shown the applicability of the
Choi criteria even in non-GIST STS\textsuperscript{27} (Fig. 2). In a study of 37 patients, Stacchiotti et al.\textsuperscript{27} compared RECIST and Choi criteria for assessing the response to treatment in high-grade STS on contrast-enhanced computed tomography (CT) and dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI). The RECIST and Choi criteria were adapted to MRI in their study by calculating the percentage of enhancement on DCE-MRI on subtracted contrast-enhanced T1-weighted images (matrix, 254 × 384; slice thickness, 5 mm; inter-slice gap, 2 mm; repetition time (TR), 616 ms; echo time (TE), 11 ms) using serial regions of interest encompassing the entire tumor and muscle as reference. A partial response was indicated by either a decrease in size of more than 10% or a decrease in attenuation on CT or enhancement on contrast-enhanced MRI by greater than 15%. In addition, functional imaging techniques such as fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography (PET)/CT are also useful in assessing the response to imatinib (Fig. 3). Imatinib causes dose-dependent fluid retention and edema, occasionally progressing to ascites and pleural effusions.

Figure 3 A 56-year-old woman with pigmented villonodular synovitis (PVNS) metastatic to the inguinal nodes and muscles of the thigh after resection of the primary tumor in the knee joint 1 year before. (a) Coronal $^{18}$F-FDG-PET/CT image of the right lower limb demonstrates an intensely FDG-avid (maximum standardized uptake value (SUV\textsubscript{max}) of 22) mass in the anterior compartment of the right thigh (arrows). (b) Coronal $^{18}$F-FDG-PET/CT image obtained 1 month after treatment with imatinib shows decreased FDG uptake of the mass with central photopenia (arrows), suggesting interval necrosis and treatment response.
which may be misinterpreted as disease progression\(^{28,29}\). Fluid retention may be seen in up to 80% of patients, especially elderly female patients with low serum albumin levels\(^{28}\). Response to diuretics and occasionally drug discontinuation can help in differentiating toxicity from disease progression.

**Other TKIs in non-GIST STS**

Sunitinib is used as a second-line agent in GIST, following primary or secondary resistance to imatinib\(^{22}\). It is a multi-targeted TKI which is FDA approved for imatinib-resistant GIST and metastatic renal cell carcinoma. In sunitinib-resistant GIST, a host of other TKIs including sorafenib, pazopanib, dasatinib and nilotinib are under research in several phase I and II trials\(^{30}\). Expecting results similar to imatinib and sunitinib in GISTs, the efficacy of multi-targeted TKI is being studied in advanced non-GIST STSs in several phase II trials. In a study of 142 patients with advanced or relapsed STS treated with pazopanib after failure with second-line chemotherapeutic agents, Sleijfer et al.\(^{9}\) found that the 12-week progression-free rate (PFR) was 44%, 49% and 39% in LMS, SS and other STS types, respectively, which were better than the response to second-line chemotherapeutic agents. In April 2012, pazopanib was approved by the FDA for the treatment of metastatic renal cell carcinoma and advanced STS (excluding adipocytic STS and GIST) that fail to respond to first-line chemotherapeutic agents.

The activity of TKIs, which are potent antiangiogenic agents, is based on the rationale that angiogenesis is key to the growth and dissemination of tumors, including STS. The formation of neovascular channels in tumors occurs in response to ischemia, which upregulates the expression of angiogenic factors such as VEGF and PDGF. VEGF is overexpressed in most sarcomas, reflecting their malignant potential and poor outcome\(^{31}\). Studies on various STSs have shown that there is a direct correlation between the tumor concentration of angiogenic factors and tumor grade, local recurrence, metastasis and overall survival\(^{31}\). Receptors of VEGF (VEGF-R1, 2, 3) and PDGF (alpha, beta-) are targets for TKI\(^{18}\) (Fig. 1). Monoclonal antibodies to VEGF have an effect similar to TKI. Bevacizumab, a humanized anti-VEGF antibody that is FDA approved for combination treatment of metastatic colorectal, renal and lung cancers, is being evaluated in phase II trials for combination treatment in STS\(^{32}\).

TKI knock off the neoangiogenic pathways in sarcomas causing progressive decrease in density and enhancement on contrast-enhanced CT without necessarily causing shrinkage of the tumor (Fig. 4). This is explained by the fact that MTTs are cytostatic agents rather than cytotoxic\(^{33,34}\). There may be an apparent increase in the size of the tumor, which may be misinterpreted as tumor progression.
progression (Fig. 5). Similarly, tumor progression can occur without actual increase in size and may be seen as new intratumoral nodules or increase in tumor attenuation\[35\] (Fig. 6). Thus, density changes on post-treatment imaging rather than size alone are more critical for assessing treatment response. The pitfalls and limitations of using RECIST alone for response evaluation at imaging in non-GIST STSs are similar to that of GIST and metastatic renal cell carcinomas (RCC)\[25,34\] (Figs. 5 and 6). Alternate tumor response criteria such as the size and attenuation CT criteria, morphology, attenuation, size, and structure (MASS) criteria for metastatic RCC and the Choi criteria for GIST have been proposed to incorporate a subjective component to response evaluation\[26,36,37\]. On similar lines, the Choi criteria have been evaluated for assessment of treatment response in high-grade STS. In a study of 37 patients with advanced STS treated with chemoradiotherapy, Stacchiotti et al.\[27\] found that the Choi criteria had greater sensitivity than RECIST for assessing tumor response.

Analyzing the metabolic tumor response based on $^{18}$F]FDG uptake according to the EORTC (European Organisation for Research and Treatment of Cancer) criteria is an attractive option, but limited by lack of standardization of uptake values\[38\].

Imaging also plays a key role in recognizing drug toxicity. TKI can cause transient increase in aminotransferases, amylase and lipase\[39\]. Imaging evaluation may be requested in such patients to exclude hepatitis or pancreatitis (Fig. 5). Pazopanib and bevacizumab have been reported to cause hepatic steatosis and hepatitis when used as monotherapy or in combination with non-hepatoxic drugs\[39\]. Sorafenib has been reported to cause painless pancreatitis diagnosed based on CT findings and increased serum lipase levels\[40\]. TKI can also cause acute acalculous cholecystitis due to gall bladder ischemia\[41\]. Bowel-related complications are known with both TKI and anti-VEGF antibodies\[42\]. TKI can cause ischemic colitis, pneumatosis and bowel perforation, which may come to attention for the first time at imaging.

Figure 5 A 78-year-old man with metastatic leiomyosarcoma. (a) Axial contrast-enhanced CT image demonstrates a lobulated heterogeneous mass along the left pelvic sidewall (arrow) representing metastatic disease. (b) Axial contrast-enhanced CT image after 6 months of treatment with pazopanib reveals increased size of the mass with a concurrent significant decrease in the density (arrow). (c) Axial contrast-enhanced CT image of the abdomen during an episode of acute abdominal pain during the course of treatment reveals a bulky and edematous pancreas with peripancreatic stranding consistent with acute pancreatitis (arrowhead), a class-specific drug toxicity of tyrosine kinase inhibitors (TKIs).
Recognizing these complications, especially in the perioperative period, becomes important and may necessitate withdrawal of the drug. Given that TKIs cause endothelial injury, it is not unusual to see arterial and venous thromboembolic phenomena, which may necessitate drug discontinuation [29].

Src intracellular kinases, which are the common point for several tyrosine kinase pathways determine tissue invasion and metastasis. Dasatinib is a new novel therapeutic agent that can inhibit multiple kinases including the Src family, BCR-ABL kinase and PDGFR [43]. Dasatinib has been shown to inhibit cell migration and promote apoptosis in sarcoma cell lines [43]. Dasatinib has been found to be useful for chronic myeloid leukemia resistant to imatinib and Philadelphia chromosome-positive acute lymphoblastic leukemia [44]. Several phase II trials are exploring the efficacy of dasatinib in metastatic STS [45] (Fig. 7). The toxicity profile of dasatinib includes myelosuppression, neuropathy, gastrointestinal effects (diarrhea, nausea, vomiting) and fluid retention. Exudative pleural effusions can occur with dasatinib in 20% of patients, requiring dose reduction, diuretics or steroid therapy [46] (Fig. 7).

mTOR driven non-GIST STS

The mTOR serine/threonine kinase is an integral part of the PI3K pathway that is activated in several mTOR driven cancers such as renal cell carcinoma, either intrinsically or by mutations in regulatory genes such as TSC1 and 2, VHL, PTEN [47]. mTOR inhibitors are a group of drugs that inhibit the mTOR cascade by binding to the mTOR complex 1 protein and include sirolimus, temsirolimus, ridaforolimus and everolimus [18] (Fig. 1). Temsirolimus and everolimus are currently FDA approved for treatment of advanced RCC. Based on the rationale that the mTOR pathway is critical even in sarcomagenesis, mTOR inhibitors are being evaluated in non-GIST STS. For example, ridaforolimus has shown encouraging results in the SUCCEED phase III trial.
for advanced sarcomas\textsuperscript{48}. Using a combination of drugs to block both the mTOR cascade and its upstream regulators such as the IGF pathway may have a synergistic effect. Quek et al.\textsuperscript{49} reported encouraging results with a combination of everolimus and figitumumab, IGF-1R monoclonal antibody, in a phase I trial in a sarcoma-predominant population.

A classic example for mTOR driven sarcoma is PEComa, a tumor of the perivascular endothelial cells. PEComas typically arise in the genitourinary tract, liver, pancreas, retroperitoneum and mesentery and affect young adult females\textsuperscript{50}. They can range from seemingly benign to malignant variants. Malignant PEComas tend to behave as aggressively as other STSs with high recurrence and metastatic rates\textsuperscript{14} (Fig. 8). Preoperative diagnosis at imaging is often difficult due to their non-specific appearance. In the uterus, benign tumors may mimic leiomyomas, whereas the malignant variants can mimic other uterine sarcomas\textsuperscript{51}. Malignant PEComas are usually large heterogeneous masses with variable enhancement and infiltration of adjacent structures. Treatment of malignant PEComas is surgical excision as they are usually resistant to chemotherapy and radiotherapy\textsuperscript{14}. In addition, targeted drugs against the mTOR cascade are under research (Fig. 8). In a study of 3 patients with PEComas treated with the mTOR inhibitor sirolimus, Wagner et al.\textsuperscript{14} found significant clinical response in all the patients.

The major toxicities of mTOR inhibitors include myelosuppression, asthenia and gastrointestinal side effects (nausea, vomiting, diarrhea, enteritis). Everolimus is rarely associated with acute cholecystitis, which is postulated to be due to ischemia related to endothelial injury\textsuperscript{52}. Discontinuation of the drug with antibiotic therapy is usually sufficient with surgery reserved for complicated cases. mTOR inhibitors are also known to cause dose-dependent non-infectious pneumonitis (NIP) in 2% to 36% of patients\textsuperscript{53} (Fig. 8). Patients can be asymptomatic or present with cough, fever and dyspnea. Imaging features usually precede clinical features and progress from non-specific ground glass opacities and septal thickening to multifocal consolidation with basilar and peripheral predominance (Fig. 8). Less commonly, diffuse alveolar hemorrhage, alveolar proteinosis and desquamative interstitial pneumonia may be encountered. NIP associated with mTOR inhibitors is graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (v4.0). Grade 1 and 2a NIP, defined as abnormal radiological findings in asymptomatic patients or patients with cough, do not need dose adjustment, but grade 2b, 3 and 4 NIP, defined as severe cough requiring oxygen may need dose reduction or drug withdrawal and steroid treatment\textsuperscript{53}. Bronchoalveolar lavage to exclude infection and pulmonary function testing with weekly high-resolution chest CT are required for monitoring the patient and excluding a malignant disease process. Immunosuppression can result in opportunistic infections. Bowel toxicity is known with mTOR inhibitors and includes enteritis and bowel perforation\textsuperscript{42}.

\textbf{Trabectedin (ET743): the drug from the sea}

Trabectedin (ET743) is a tetrahydroisoquinoline alkaloid, originally extracted from a marine tunicate, that
binds to and inhibits DNA transcription preventing the progression of the cell cycle beyond the G2/M phase\textsuperscript{54} (Fig. 1). Several phase II clinical trials have evaluated the efficacy of trabectedin in non-GIST STS including LPS, LMS, SS but the maximum response was seen in myxoid LPS and LMS\textsuperscript{7,55} (Fig. 9). Approved for second-line treatment of metastatic STS in Europe, trabectedin has been shown to result in more than 20% progression-free survival after 6 months of treatment although the objective response as per the World Health Organization (WHO) criteria was not satisfactory\textsuperscript{56}.

**Figure 8** A 68-year-old man with metastatic malignant renal PEComa 3 years after nephrectomy. (a,b) Axial unenhanced CT images of the pelvis before (a) and 1 month after the start of treatment with everolimus (b) reveals a decrease in the size of a metastatic deposit in the rectovesical pouch (arrows). (c) Axial CT image of the lung bases at baseline demonstrates no abnormality. (d) Axial CT image of the lung bases 1 month after the start of everolimus treatment shows rapid interval development of interlobar septal thickening and ground glass opacities with basilar and peripheral distribution consistent with everolimus-induced interstitial pneumonitis, a class-specific drug toxicity of mTOR inhibitors. The patient was symptomatic, with shortness of breath. (e) Follow-up CT of the chest 3 months after discontinuing everolimus and initiating steroid therapy demonstrates improvement in the interstitial lung toxicity.
Myxoid/round cell LPS is the second most common variant of LPS and is associated with aggressive behavior and higher risk of metastasis, especially if the round cell component is higher \(^5\). Round cell LPS is now considered as a spectrum of myxoid LPS as both have a common translocation t(12; 16)(q13; q11) in excess of 90% of cases resulting in the formation of a chimeric fusion protein FUS-CHOP \(^2,16\). Myxoid LPS is a well-demarcated tumor at imaging with fluid characteristics on both CT and MRI \(^5\). The pathognomonic features at MRI include microscopic fat-containing septae and diffuse enhancement after contrast administration. The amount of macroscopic fat is, however, minimal. Myxoid LPS has a tendency to metastasize to serosal membranes, paraspinal locations and the retroperitoneum \(^5\).

Localized LPSs are treated with surgery and radiotherapy with a relapse rate of about 40\% \(^5\). For advanced and metastatic LPS, trabectedin has shown significant efficacy in most phase II trials. The response rate of LPS to trabectedin by RECIST is variably reported as 24—51\% \(^7,58\). The mechanism of action of trabectedin is unknown, but in the case of myxoid LPS, it is postulated that trabectedin inactivates the fusion oncogene FUS-CHOP and removes the block in the cell cycle, thereby promoting differentiation of tumor cells \(^5\). This manifests pathologically as replacement of the cellular tumor component by acellular stroma and a decrease in tissue density \(^7\). At imaging, treatment response is indicated by a decrease in tumor density with or without tumor shrinkage \(^5\) (Fig. 9). An unusual form of treatment response observed in some cases of LPS is a progressive increase in the amount of macroscopic fat with no appreciable change in tumor size, in contrast to minimal or no fat on the pretreatment scan, representing differentiation in dedifferentiated components (Fig. 10). Trabectedin is usually well tolerated; neutropenia, thrombocytopenia and transient increase in transaminases are common adverse effects. Capillary leak syndrome has been described with the use of trabectedin, which manifests as unilateral pulmonary edema and anasarca \(^5\) (Fig. 10).

**MTT in miscellaneous STSs**

Alveolar soft part sarcoma (ASPS) is an uncommon vascular mesenchymal tumor affecting the lower extremities in young adults \(^6\). They have a high tendency to metastasize most often to the lungs, liver and central nervous system. Metastatic lesions respond poorly to
conventional therapy. ASPSs belong to the group of MiT tumors that are associated with activation of microphthalmia-associated transcription factor (MiT) and upregulation of the c-Met gene. A characteristic translocation t(X; 17) seen in more than 90% of cases of ASPS is responsible for upregulation of c-Met, which plays a key role in the angiogenesis of ASPS[16,61]. Inhibitors of c-Met and antiangiogenic factors are under investigation in various trials[62].

The heterogeneous group of small round cell tumors including skeletal and extraskeletal Ewing sarcoma constitutes the Ewing sarcoma family of tumors (ESFT)[63]. Adult ESFTs often tend to be extraskeletal and can arise anywhere from the head to the extremities. Metastases are present in up to 31% of patients at the initial diagnosis, usually in the lungs and bone/bone marrow[64]. The standard of care for ESFT is neoadjuvant chemotherapy with conventional agents followed by radiation and surgery. Recognition of a characteristic translocation t(11; 22) in 85% of cases of ESFT has created interest in MTT for these tumors[16]. The transcriptional product of this translocation EWS-FLI1 causes upregulation of IGF1. Figitumumab, a monoclonal antibody against the IGF1-receptor has shown benefit in the preliminary phase I data[65] (Fig. 1).

**Conclusion**

Advanced and metastatic STSs are challenging to manage due to poor response to conventional chemotherapy. Several non-GIST STSs have characteristic genetic

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**Figure 10** A 54-year-old woman with well-differentiated liposarcoma containing dedifferentiated components. (a) Axial contrast-enhanced CT image before the start of treatment demonstrates well-differentiated fat anteriorly (white arrows). The dedifferentiated component is seen as ill-defined soft tissue attenuation areas posteriorly (white arrowheads) with enhancing solid nodules (black arrow). (b) Axial contrast-enhanced CT image 12 months after treatment with trabectedin reveals replacement of the dedifferentiated component (white arrowheads) as well as the soft tissue nodule (black arrow) with fatty tissue suggestive of treatment effect or further differentiation in previously dedifferentiated components. The well-differentiated component (white arrow) is unchanged. (c) Axial CT image of the chest during the course of treatment when the patient developed an episode of fever and cough demonstrates interlobar interstitial thickening in the right lung base representing unilateral pulmonary edema, seen with capillary leak syndrome, a known complication of trabectedin therapy.
alterations that can be targeted at a molecular level in patients who have failed conventional chemotherapy. Following the success of imatinib in GISTs, many more sarcomas are being treated with MTT. The use of these drugs will increase in the future and make the role of radiologist critical in assessing treatment response. Similar to GIST, response of non-GIST STS to MTT tends to be different from other solid tumors treated with conventional chemotherapeutic agents, which necessitates the use of alternate response criteria. A decrease in tumor density with or without tumor shrinkage is often seen with most of the targeted therapies. Recognizing class-specific drug toxicities at imaging is important for appropriate patient management.

Conflict of interest
The authors have no conflicts of interest to declare.

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