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Contemporary management of metastatic soft tissue sarcoma

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ABSTRACT

Soft tissue sarcoma (STS) is a rare, heterogeneous cancer that can have high rates of distant metastases. Optimal treatment planning requires detailed knowledge of distinct sarcoma histologies as well as the wide array of therapeutic options through surgical, medical, radiation, and interventional oncology. In this review article, we discuss the contemporary management of metastatic STS and the underlying data behind these recommendations. All patients with metastatic STS should be discussed in a multidisciplinary tumor board at an experienced sarcoma center. For patients with oligometastatic disease, there should be strong consideration for definitive local therapy such as surgical resection, stereotactic body radiation therapy, or ablative procedures. In cases with widespread metastases, cytotoxic chemotherapy represents the standard treatment for STS patients with traditional chemotherapies, such as anthracyclines, gemcitabine/docetaxel, ifosfamide, and dacarbazine, still being the most commonly used drugs today. The recent approvals of trabectedin, eribulin, and pazopanib have expanded the therapeutic armamentarium for metastatic STS. Histology-directed treatment is crucial for certain subtypes of STS which are highly sensitive to targeted therapy and relatively insensitive to chemotherapy. Despite the significant progress that has been made in metastatic STS in the past decade, overall prognosis is poor and there is a critical need for novel therapeutics.

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Introduction

Soft tissue sarcomas (STS) are generally diagnosed while still in the local stage with only 14% of patients presenting with metastatic disease at diagnosis.[1] However, approximately 35% of patients with optimally treated localized disease will develop distant metastases within 5 years.[2] STS have generally been treated with cytotoxic chemotherapy with modest efficacy when compared to other tumor types (breast, lung, colorectal, lymphoma, etc.). One of the challenges of treating STS is that STS encompasses a wide heterogeneity of distinct biological processes with differing natural history and therapeutic responsiveness. For example, high-grade synovial sarcoma is an aggressive disease with high metastatic rates that responds well to cytotoxic chemotherapy. On the other hand, alveolar soft part sarcoma (ASPS) is a chemoresistant histology with a high rate of metastases, however, it has an indolent time course and responds readily to vascular endothelial growth factor (VEGF) inhibition. Understanding the differences between these behaviors is key in the treatment of metastatic STS. The key modalities in the treatment of metastatic sarcoma involve cytotoxic chemotherapy, targeted therapy, surgical metastectomy, and local ablative procedures (Fig 1).

Patterns of metastatic spread

STS predominantly metastasizes to the lungs with up to 52% of metastatic patients presenting with isolated pulmonary metastasis.[3,4] Other sites of metastasis include the liver, bones, and brain. Retroperitoneal sarcomas also have high rate of metastasis to the liver.[5] Lymph node metastasis are rare, occurring in $<3\%$ of cases.[6] Therefore, when mildly enlarged or PET avid regional lymph nodes are seen on staging scans, the presumption should be that they are reactive and not malignant. Exceptions to this include angiosarcoma, embryonal rhabdomyosarcoma, and epithelioid sarcoma, where the incidence of lymph node metastases is approximately 15%. A high index of clinical suspicion should warrant a biopsy or surgical excision during primary resection, as radical lymphadenectomy for lymph node metastasis is potentially associated with a 4-fold increase in overall survival time.[6] Myxoid liposarcoma has a peculiar pattern of metastatic spread where extrapulmonary spread is of chief concern.[7] The rates of skeletal metastasis approaches 50% and there is evidence that MRI full spine should be performed to exclude occult spinal metastases at diagnosis.[8]

Local therapy

All patients with metastatic STS should be discussed in a multidisciplinary tumor board at a major referral center. There are a certain percentage of patients with oligometastatic disease who may potentially have a long period of relapse-free survival or be cured. For pulmonary oligometastases, multiple studies have shown long-term survival after resection of isolated pulmonary nodules in select patients. In a single institution study at Memorial Sloan Kettering Cancer Center, 803 patients underwent pulmonary metastectomy with a 5-year survival of 34%, median overall survival of 33.2 months, and a median time to recurrence of 6.8 months.[9] Factors associated with improved outcomes were leiomyosarcoma (LMS) histology, solitary lung metastasis, increased time from primary resection to development of metastases, and primary tumor size $\leq$10 cm. A European review of 255 patients undergoing pulmonary metastectomy showed a 5-year overall survival rate of 38% with positive prognostic factors being disease-free interval of $>$2.5 years, age $<$40 years, and Grade I/II tumors.[10] Other single institution studies of pulmonary metastectomy have reported 5-year survival rates ranging from 23% to 50%.[11-15] These data strongly suggest that select patients with oligometastatic disease should be considered for pulmonary metastectomy. Criteria for patient selection should include patient performance status, feasibility of complete resection, rapidity of disease progression, and length of disease-free interval. Studies of repeat resection after recurrence following primary pulmonary metastectomy

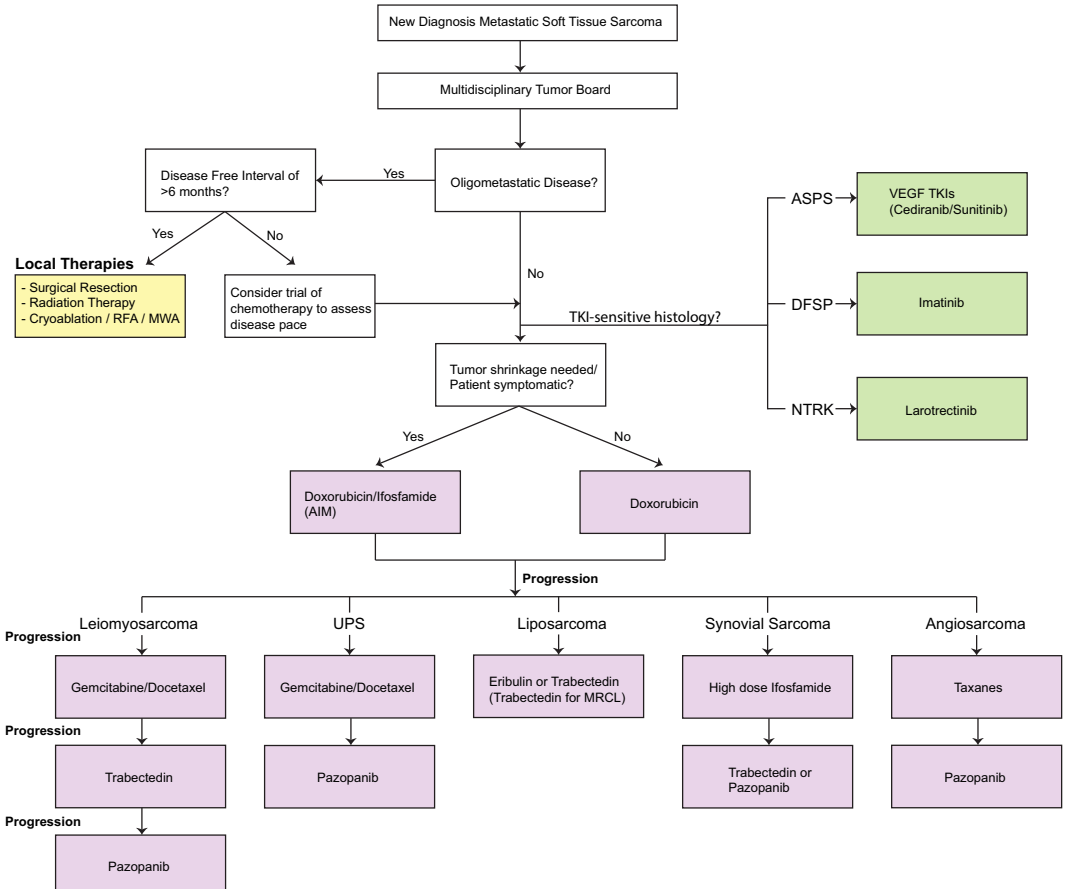

Fig. 1. Treatment algorithm for metastatic soft tissue sarcoma.

have shown that approximately 30% of patients will have prolonged survival,[16,17] suggesting that repeat pulmonary reresection is feasible in appropriately selected patients. It must be noted that all of these studies are retrospective studies of highly selected patients and will not apply to the general metastatic sarcoma patient population. Careful curation of patients is needed to ensure optimal outcomes.

For patients who are not candidates for surgical metastectomy, stereotactic body radiotherapy (SBRT) and local ablative procedures have proven effective in control of metastatic sites. In a study of 44 patients with 117 pulmonary metastases treated with SBRT at 50 Gy, the local control rate was 95% and the 5-year overall survival was 50%.[18] Twenty-seven percent of patients developed new metastases and underwent further SBRT. Multiple other series of SBRT for pulmonary metastases show excellent local control rates (82%-96%) and minimal toxicity.[19-22] Local ablative treatment options performed by interventional radiology include percutaneous radiofrequency ablation (RFA), microwave ablation, and cryoablation. These ablative therapies are generally more effective with lesion sizes less than 3 cm.[23,24] In a study of 46 STS patients with 144 lung metastases, RFA achieved a local control rate of 85% and median overall survival of 31.7 months.[25] One- and three-year overall survival rates were 80.6% and 47.1%, respectively. The most common complication was pneumothorax. This data are similar to another study of 22 patients with 55 pulmonary metastases, measuring 0.5-2 cm, treated with RFA where the local control rate was 95%, 3-year survival rate was 85%, and pneumothorax rate was 10%.[26] More recently, microwave ablation and cryoablation have become the more commonly used ablation modalities for treatment of lung metastases, although no studies specific to STS lung metastases have been reported for either.[23,24]

Liver metastases are more common in retroperitoneal sarcomas and gastrointestinal stromal tumors. There is limited data on whether hepatic resection and/or percutaneous embolization for oligometastases prolongs survival but there are a few small published series that suggest long-term survival can be achieved for a subset of patients.[27-30] However, in these series when compared to pulmonary metastases, the rates of subsequent recurrence appear to be higher. For patients with multifocal liver-dominant metastases, image-guided transarterial therapies, including chemoembolization and radioembolization, may be considered. In a multicenter study, 37 patients with STS liver metastases and 2 patients with primary hepatic STS were treated with radioembolization using yttrium-90 microspheres.[31] Disease control and objective response rates were 77% and 36%, respectively. Median overall survival was 30 months. In a single-center study of 30 STS patients with liver metastases treated with chemoembolization, median overall survival was 21.2 months and progression-free survival (PFS) was 6.3 months. At our institution we consider local therapy for all patients with limited hepatic metastases and controlled extra-hepatic metastases.

In determining local treatment strategy, factors to consider include proximity to critical normal tissues (including heart, diaphragm, and bowel), tumor size, number of lesions, previous local therapy to the area in question, patient candidacy for undergoing anesthesia and ability to tolerate invasive procedures, and potential risk of complications including high likelihood of pneumothorax. SBRT has the advantage of being able to be used in the treatment of sites for which surgery and RFA may not be possible. However, cumulative radiation dose to the lungs and other critical structures must be considered to determine the safety of treating a large number of lesions with SBRT. To date, no prospective trials comparing SBRT, surgery, and other local therapies for metastatic sarcoma have been performed.

Cytotoxic chemotherapy

Cytotoxic chemotherapy is the mainstay of metastatic STS treatment. Commonly used drugs include anthracyclines, gemcitabine, and taxanes. Tumor shrinkage is generally not solely relied upon as a measure of effectiveness due to the fact that chemotherapy can result in acellular, nonviable tissue that does not readily shrink on radiologic imaging. This is demonstrated by a

study of 42 patients with STS that underwent neoadjuvant chemotherapy ± radiation therapy where the RECIST response rate was only 5% (all partial response) but 19% of patients had ≥95% pathologic necrosis.[32] The sensitivity of RECIST to predict pathologic response was only 25%. Therefore, PFS is increasingly used as a meaningful marker of benefit for STS trials. It is crucial to keep this context in mind when treating metastatic STS, as the response rates for the most intensive therapy of doxorubicin/ifosfamide (26%[33]) pales in comparison to response rates for other tumor types, for example lymphoma (R-CHOP 78%[34]), colorectal cancer (FOLFOXIRI 65%[35]), breast cancer (palbociclib/letrozole 55%[36]), etc. It is also important to note that the rarity and wide heterogeneity of STS lends itself to clinical trials where multiple histologies are consolidated together, making it difficult to separate natural history vs chemotherapy effectiveness. Indeed, previous work has shown that the survival time of metastatic sarcoma is better predicted by natural history of the histologic type rather than response to chemotherapy.[37]

Anthrayclines have been the standard backbone for first-line therapy in metastatic STS. Intensification of therapy with the addition of ifosfamide (AIM) is the standard regimen for adjuvant therapy; however, its use in the metastatic setting is limited due to increased toxicity and no improvement in survival. This was demonstrated by the EORTC 62012 trial which randomized patients to doxorubicin monotherapy vs doxorubicin/ifosfamide and showed no significant difference in overall survival (12.8 vs 14.3 months) despite an improvement in median PFS (4.6 vs 7.4 months) and overall response rate (14% vs 26%).[33] There was significantly increased toxicity with AIM therapy with a tripling of the febrile neutropenia rate (13% vs 46%), increased grade 3/4 anemia (5% vs 35%), and thrombocytopenia (<1% vs 33%). These findings are similar to the PICASSO III trial of doxorubicin vs doxorubicin/palifosfamide.[38] We sometimes consider AIM therapy first line if there is an urgent need for tumor shrinkage or symptom control and patients are able to tolerate this regimen.

The addition of olaratumab, a monoclonal antibody to platelet-derived growth factor receptor alpha (PDGFRα), to doxorubicin temporarily marked a milestone in the treatment of metastatic STS, with a randomized phase II study showing an astounding near doubling of median overall survival (26.5 vs 14.7 months) despite a modest increase in PFS (6.6 vs 4.1 months) and response rate (18% vs 12%).[39] There was also no correlation between survival and the level of PDGFRα expression in tissue. These data led to accelerated FDA approval in October 2016 and established doxorubicin/olaratumab as the therapy of choice for front-line treatment. However, the confirmatory randomized phase III ANNOUNCE trial resulted on January 22, 2019 showed that the addition of olaratumab had failed its primary outcome, with reduced median PFS (5.4 vs 6.8 months) and ORR (14% vs 18.3%), and no difference in overall survival (hazard ratio [HR] 1.047, P= 0.69). The FDA announced a few days later that olaratumab should not be initiated in new STS patients outside of a clinical trial.[40]

Gemcitabine/docetaxel is an effective treatment regimen for STS, particularly for patients with uterine LMS or undifferentiated pleomorphic sarcoma (UPS, formerly malignant fibrous histiocytoma). Early data from a 34-patient cohort of mainly uterine LMS showed a 53% overall response rate and a median time to progression of 5.6 months.[41] This finding was confirmed in a larger randomized study of gemcitabine alone vs gemcitabine/docetaxel in all STS patients where there was an increased response rate from combination therapy (8% vs 16%) as well as median PFS (3.0 vs 6.2 months) and overall survival (11.5 vs 17.9 months).[42] The response rate for gemcitabine/docetaxel was especially enhanced in LMS (17%) and UPS (36%).

One important question is whether anthracyclines or gemcitabine/docetaxel are superior in the front-line setting for metastatic STS. This head-to-head comparison was recently published in 2017 via the GeDDis trial, which accrued 257 treatment naïve patients with metastatic STS and randomized them to doxorubicin vs gemcitabine/docetaxel.[43] The primary outcome was PFS at 24 weeks and there was no significant difference between the 2 groups (doxorubicin: 46.3% vs gemcitabine/docetaxel 46.4%). There was also minimal difference in overall response rate (19% vs 20%) and overall survival (76.3 vs 67.3 weeks). Interestingly, there was no superiority for gemcitabine/docetaxel in either the LMS (HR 1.06), uterine LMS (HR 1.06), or UPS (HR 1.00) cohorts. Gemcitabine/docetaxel was actually more difficult to administer than doxorubicin, with significantly decreased mean dose intensity (83.4% vs 93.7%) and more dose delays (56% vs 46%). This

may have been due to the treatment schedule for gemcitabine/docetaxel, with gemcitabine given on D1 and gemcitabine/docetaxel given on D8, leading to a higher probability of cytopenias on D8 and thus leading to dose omissions or delays. This is in contrast to doxorubicin, which is given once every 3 weeks. It is important to note that the doses of gemcitabine/docetaxel were intentionally lower in the GeDDis trial as compared to earlier trials (gemcitabine dose reduced from 900 mg/m^2 to 675 mg/m^2 and docetaxel reduced from 100 mg/m^2 to 75 mg/m^2) due to toxicity concerns. Whether this resulted in inferior performance is unclear, however, the resulting decreased dose intensity with the lower dose suggests that higher dosages were unlikely to be feasible. One alternate modification that we practice here for certain patients is spacing out the dosing interval to D1 and D15 of a 30-day cycle, maximizing the dose of gemcitabine to 1500 mg/m^2 while decreasing the dose of docetaxel to 50 mg/m^2, and administering both drugs at each dosing day. This is based off of the Axtell regimen,[44] which had a high response rate (31.4%) across STS and significant decrease in cytopenic toxicity compared to the every 3-week regimen. We consider this regimen for patients who we think may have trouble tolerating the D1/D8 regimen.

Dacarbazine is an older drug which has modest single-agent activity in sarcoma. Early studies of single-agent high-dose dacarbazine for STS patients resulted in ORR around 7.5%-18% with the main toxicity being hematologic suppression.[45-47] Dacarbazine is also used in combination with other active agents such as doxorubicin/dacarbazine,[48] doxorubicin/dacarbazine/ifosfamide (MAID),[49] and gemcitabine/dacarbazine[50] with effective results. Given its place as an older drug, dacarbazine has frequently been used as a comparator arm for phase III trials of newer agents.[51-53] Temozolomide is an oral analogue of dacarbazine which has similar activity with ORR 5%-15% but has a more convenient route of administration.[54-57] We generally reserve dacarbazine/temozolomide for later lines of therapy for treatment refractory patients.

Recent developments

Within the past 7 years, there has been tremendous progress in the systemic treatment of STS, manifested by FDA approval of multiple drugs. In 2012, the first drug to come onto the market was pazopanib, an oral inhibitor of vascular endothelial growth-factor receptors (VEGFR-1, -2, and -3), PDGFR-α/β, and fibroblast growth-factor receptors 1 and 3. In the phase III PALETTE trial of pazopanib 800 mg vs placebo there was a significant increase in median PFS of 4.6 vs 1.6 months.[58] The overall response rate was low at 6% for pazopanib vs 0% for placebo. Of note, liposarcomas were not included due to low efficacy seen in the prior phase II trial.[59] The most common dose-limiting side effect seen in practice is diarrhea which can be debilitating for patients. In the phase III trial the incidence of diarrhea was 58% in the pazopanib group and 16% in the placebo group. To mitigate this, we start at a low dose of 200 mg and titrate up by 200 mg every few days until 800 mg is reached or patient has intolerable diarrhea despite best supportive measures. Other common side effects are nausea (54%), hypertension (41%), hair hypopigmentation (38%), and dysgeusia (27%).

Trabectedin was the next drug approved in 2015 for LMS and liposarcoma. The pivotal phase III trial of trabectedin was compared to dacarbazine, and demonstrated a significant increase in PFS (mPFS 4.2 vs 1.5 months, HR 0.55).[52] Overall response rate was modest at 9.9% for trabectedin and 6.9% for dacarbazine. Trabectedin is an intravenous cytotoxic chemotherapy and its side effects are similar to other cytotoxic drugs with high rates of neutropenia (49%), anemia (39%), and thrombocytopenia (30%). Other notable side effects are transient transaminitis (ALT increase grade 3/4 26%) and myopathies (creatine phosphokinase elevation grade 3/4 5.3%, rhabdomyolysis 1.2%). Logistically, trabectedin is a 24-hour IV infusion which requires central venous access and a pump for patients to bring home. Trabectedin has also been found to be effective in translocation-associated sarcomas, especially myxoid/round cell liposarcoma. A retrospective review of 51 patients with pretreated myxoid liposarcoma treated with trabectedin demonstrated an overall response rate of 51% and a median PFS of 14 months.[60] Laboratory work has elucidated that the mechanism of action of this exquisite sensitivity is due to a block of the binding

of the FUS-CHOP fusion oncogene to DNA promoters.[61] Efficacy in other translocation-associated sarcomas was demonstrated in a randomized phase II study of trabectedin vs best supportive care in 76 patients.[62] The majority of patients had myxoid/round-cell liposarcoma (32%) or synovial sarcoma (25%). The PFS was significantly increased (5.6 vs 0.9 months, HR 0.07) as was the overall response rate (8% vs 0%).

Eribulin is a microtuble inhibitor that was FDA approved for liposarcoma in 2016. This was based on a phase III trial of 452 LMS and liposarcoma patients randomized to eribulin or dacarbazine which showed a significant improvement in overall survival of 13.5 vs 11.5 months (HR 0.77).[51] Interestingly there was no difference in progression-free survival (mPFS 2.6 vs 2.6 months) or overall response rate (4% vs 5%). Subgroup analysis clearly showed that the benefit was driven entirely by the liposarcoma cohort, which had a substantial improvement in overall survival (15.6 vs 8.4 months) and a lesser degree in PFS (2.9 vs 1.7 months), suggesting that there may be an indirect influence on the benefit of subsequent therapies. These data led the FDA to approve eribulin only for liposarcoma. Side effect profile of eribulin is similar to other microtubule inhibitors with a high degree of neutropenia (43%), alopecia (35%), and peripheral neuropathy (19%).

Histology-directed therapy

Although STS encompasses over 50 types of distinct biological types, the rarity of the disease lends itself toward consolidating histologies for the purposes of clinical trials. It is clear that certain histologies behave differently than others and that treatment ideally would be directed at histologic type. Below, we will discuss treatment strategies for specific tumor types.

Synovial sarcoma

Synovial sarcoma is an aggressive sarcoma that has a high propensity to metastasize. Compared to other STS, it is especially sensitive to chemotherapy, particularly with alkylating agents. After first-line anthracycline therapy, we prefer high-dose ifosfamide at doses $\geq$10 g/m^2. Prior publications have noted response rates ranging from 36% to 100%.[63-65] Ifosfamide is a difficult drug to administer as it must be given over multiple consecutive days and requires mesna administration and intensive hydration due to risk of hemorrhagic cystitis. Practically, ifosfamide can be given through an infusional pump (with mesna) that the patient takes home or as a daily infusion in the infusion center with IV or PO mesna given. Common adverse events are cytopenias with low but serious risks of hemorrhagic cystitis and neurologic toxicity. Other effective agents include trabectedin (for translocation associated sarcomas) and pazopanib.

Angiosarcoma

Angiosarcomas are sarcomas of the vasculature which generally arise in the skin/scalp or superficial soft tissue. Radiation-associated angiosarcomas, although rare, are most commonly seen in the breast after prior irradiation for breast cancer. Angiosarcomas have been found to be exquisitely sensitive to taxanes with studies showing response rates as high as 62% for single-agent paclitaxel, even in heavily pretreated patients.[66-68] Responses are more frequently seen for cutaneous angiosarcomas than for other subtypes. Weekly paclitaxel is usually given at 80 mg/m^2 and is very well tolerated with much less bone marrow suppression than anthracyclines, alkylators, or other agents used in sarcomas. This is important in the context of scalp angiosarcomas which generally occur in elderly patients (median age 79).[69] Given the vasculature nature of angiosarcoma, VEGF inhibitors have also been extensively studied, however with modest results. Single-agent bevacizumab showed initial promise[70] but the addition of beva-

cizumab to paclitaxel did not improve outcomes when compared to paclitaxel alone in a randomized phase II study.[71] Small case studies of pazopanib, an oral VEGFR TKI, have shown treatment responses[72,73] but a larger study of 8 patients showed no benefit and significant toxicity.[74] Single-agent sorafenib has also shown limited responsiveness in angiosarcomas.[75-77] A current trial with a monoclonal antibody to endoglin (TRC105) with pazopanib showed encouraging results for angiosarcoma in a phase I/II trial and is currently undergoing a large phase III trial (NCT02979899).[78]

Alveolar soft part sarcoma

ASPS is a rare STS diagnosed primarily in younger patients (median age 22) that has an indolent rate of growth yet has an extremely high rate of metastasis estimated around 57%.[79] Due to the slow nature of disease, metastases can present many years later and patients with metastatic disease can live for a prolonged period of time. ASPS is also one of the rare sarcomas that has a penchant to metastasize to the brain and high suspicion must be kept for any new neurologic symptoms. ASPS is notoriously insensitive to chemotherapy with previous reports showing a 0% response rate.[80,81] VEGFRs have emerged as a powerful treatment option for ASPS with cediranib and sunitinib showing response rates ranging from 35% to 55%.[82,83] An ongoing phase III trial of the VEGFR TKI anlotinib is currently recruiting patients with ASPS (NCT03016819). Immunotherapy is also showing early promise with a recent phase II trial of atezolizumab demonstrating an impressive response rate of 42% in ASPS patients (NCT03141684).[84]

Dermatofibrosarcoma protuberans

Dermatofibrosarcoma protuberan (DFSP) is a cutaneous STS that is low to intermediate grade, with the intermediate grade tumors denoted as fibrosarcoma (DFSP-FS). These tumors can be locally aggressive although they rarely metastasize. The molecular hallmark of DFSP is a COL1A1/PDGFB fusion gene which makes them exquisitely sensitive to TKIs that inhibit the PDGF receptor. Imatinib is the standard first-line treatment with phase II trials showing a response rate of 46% and a median time to progression of 1.7 years.[85] The aggressive fibrosarcomatous variant of DFSP also responds to imatinib but the responses are much shorter lived (response rate 70%, median PFS 11 months).[86] Sunitinib has been shown to be effective after imatinib failure, with a retrospective study noting a response rate of 40% and a mPFS of 22 months for the patients who had a radiologic response.[87]

Neurotrophic receptor tyrosine kinase-fusion sarcomas

The modern era of genomic sequencing has brought the promise of personalized treatments to the forefront of oncology. The first FDA approval for a genomically driven, histology independent drug was for the neurotrophic receptor tyrosine kinase (NTRK) inhibitor larotrectinib in November 2018.[88] In a diverse group of 55 patients with treatment refractory cancer, the response rate was an astounding 80% with durable response (median duration not yet reached with median follow-up of 8.3 months).[89] STS represented the second most common tumor type (20%), the third most common tumor type was infantile fibrosarcoma (which has a pathognomonic ETV6-NTRK3 fusion), and there were 3 gastrointestinal stromal tumors patients (5%). In our practice, we send sequencing on all of our STS to look for NTRK fusions as well as any other potentially targetable mutations (eg, microsatellite instability, ALK fusions).

Conclusions

Metastatic STS is a heterogeneous disorder with overall poor prognosis. A small percentage of metastatic patients can potentially be cured with aggressive local therapy and we strongly

encourage all patients to be initially discussed at multidisciplinary tumor board discussion at an experienced sarcoma center. However, for the vast majority of metastatic STS patients, the cancer journey encompasses multiple rounds of toxic therapy with varying efficacy. Although there has been tremendous progress in the past decade, there is still a desperate need for novel therapeutics.

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