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Advances in the Systemic Treatment of Cutaneous Sarcomas

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Abstract

Cutaneous sarcomas are a rare sub-set of soft tissue sarcomas. These tumors are managed with definitive surgical resection however upon unresectable recurrence or metastatic spread, systemic therapy is warranted in their treatment. As with other sarcomas, these treatments have classically included cytotoxic chemotherapy programs that were associated with variable response rates and poor overall survival. Recently, major advances have been made in the understanding of the molecular biology these tumors and as such treatment paradigms are changing. Multiple growth pathways have been documented to be important in the growth of cutaneous sarcomas, including receptor tyrosine kinases such as platelet-derived growth factor receptor, insulin-like growth factor receptor and c-KIT. Dysregulated angiogenesis, through VEGF and other pathways, is associated with the growth of these tumors. As such, new treatments have entered the clinical arena and a host of novel therapies are in clinical development. In this review, we discuss the current standard therapies of cutaneous sarcoma and discuss the recent advances and on-going investigations into cutaneous sarcoma biology.

Keywords

Cutaneous sarcomas; Angiosarcoma; Dermatofibrosarcoma protuberans; Kaposi's sarcoma;
Cutaneous leiomyosarcoma; Chemotherapy; Targeted therapy; Angiogenesis

Introduction

Soft tissue sarcomas (STS) are a diverse collection of mesenchymal neoplasms with an incidence of 30 per million or approximately 13,000 cases annually in the United States¹. Approximately 50% of STS develop in the extremities the while the remainder arise in the soft tissue of thorax and abdomen². Cutaneous sarcomas are a small subset of soft tissue sarcomas. As with other soft tissue sarcomas, most cutaneous malignant sarcomas are cured by surgical excision. While local recurrence following excision is not uncommon, few cutaneous sarcomas metastasize. The management of cutaneous sarcomas rarely requires the use of systemic therapy. However, in cases of unresectable or recurrent unresectable disease, systemic therapy is required. Even as recently as five years ago, it would not have been possible to differentiate the chemotherapy programs used to treat the various subtypes of cutaneous sarcomas. More recently however, developments in molecular profiling, such as the use of gene array and tyrosine kinase profiling, have allowed for the identification of oncologic driver mutations and epiphenomenon that have facilitated the development of rationally targeted novel therapies. As such, a new spectrum of agents, such as tyrosine kinase inhibitors, monoclonal antibodies and small molecule inhibitors, now allow for a more specific treatment of each of the major subtypes of cutaneous sarcomas (**Figure 1**). A limiting factor in the pace of development of these promising therapies is the relative low incidence of cutaneous sarcomas in comparison to their soft-tissue counterparts. As such, the advances in the management of cutaneous soft-tissue sarcomas lag somewhat behind that of soft-tissue sarcomas more generally. This overview will consider mainly the more common

sarcomas affecting skin. These include angiosarcoma, dermatofibrosarcoma protuberans, Kaposi's sarcoma and cutaneous leiomyosarcoma. Differential diagnoses of these neoplasms are often challenging and frequently require the integration of clinical, morphological, immunophenotypical and molecular techniques to provide an accurate diagnosis.

ANGIOSARCOMA

Angiosarcomas (AS) are a heterogeneous group of vascular neoplasms that constitutes 1% of soft tissue sarcomas³. AS, which are most commonly characterized by immunohistochemical staining for CD31, commonly arising on the face or scalp. AS are divided into multiple sub-categories including primary cutaneous angiosarcoma, radiation-associated angiosarcoma, primary-breast angiosarcoma and soft-tissue angiosarcoma. Most cases of AS are sporadic however a common clinical presentation of AS is development of a breast lesion after radiation treatment for breast cancer⁴ or in the setting of lymphedema⁵. Unfortunately, even with wide excision and irradiation, AS are generally highly aggressive and have a propensity for local recurrence, multifocal spread and early hematogenous dissemination. As such, the clinical course of AS patients is characterized by a poor overall survival with 5 year survival in the range of 10-30%^{6,7}.

Of the different subtypes of AS, cutaneous AS is the most common with one-third of AS occurring in skin⁸. Most cutaneous AS are sporadic, presenting in the scalp or face of elderly patients⁹. The prognosis of sporadic cutaneous AS correlates with high/low risk groups based on age, epithelioid histology, necrosis and tumor death¹⁰. Epithelioid angiosarcoma is a highly malignant vascular neoplasm originally recognized in the skin by Rosai¹¹. It is considered a rare variant, accounting for about 12 percent of cutaneous AS.

Etiologic factors for cutaneous AS of face and scalp remain poorly understood¹². Radiation-associated AS following treatment for breast cancer is well established as a known etiologic factor. Additional etiologies include predisposing conditions, such as chronic lymphedema. Radiation-associated angiosarcoma typically present as a cutaneous lesion several years post-therapy. The latency period for radiation-associated mammary angiosarcomas may be as brief as three years, in contrast to the other radiation-associated sarcomas⁹. Radiation-associated AS is now recognized as an important, although rare, complication of radiation treatment, with a cumulative index of 0.9 per 1,000 cases during 15 years¹³.

The clinical behavior and morphologic features of radiation-associated angiosarcoma are reportedly comparable to those of sporadic AS¹⁴. However, in the series published by Gladdy et al., radiation-associated sarcomas had a significantly worse outcome than sporadic soft-tissue sarcomas independent of histologic subtype¹⁵. This heterogeneity in clinical presentation may suggest that different molecular pathways are driving the process of angiosarcomagenesis. This has been further evaluated using transcriptional profiling to guide the search for mutations in key angiogenesis genes. In this manner, an association between KDR- (also known as VEGFR-2) positive genotype and distinct clinical presentation of AS were discovered¹⁶. These KDR mutant tumors appear to occur in the same anatomic location, either breast or chest wall, as primary lesions of the breast or secondarily to prior radiation. Further analysis and larger sample size will eventually help to clarify if KDR mutation is characteristic only for this clinical AS subset. Transcriptional profiling has also further defined the differences between primary and secondary AS. It is well understood that secondary AS, but not primary AS, have distinct 8q24 chromosomal gains due to *MYC* amplification¹⁷. Additionally *MYC* amplification has not been observed in radiation-induced atypical vascular lesions or other radiation-associated sarcomas. Similarly, coamplification of *FLT4* (which encodes VEGFR3) with *MYC* was identified in 25% of secondary AS, but not in other vascular lesions¹⁸. Interestingly, KDR mutant and

coamplified MYC/FLT4 tumors have each been shown to be responsive to anti-angiogenesis directed therapies. As such, these findings suggest new avenues for specific therapeutic targeting in AS and may have implications toward targeting angiogenesis more broadly in other tumor types.

VEGF is known to have a central role in the vascular response, growth rate, and endothelial tube formation (angiogenesis) in human tumors¹⁹ and as such there is significant interest in understanding the pathways regulating VEGF expression. Unfortunately, to date in angiosarcoma these remain largely unknown. Classically, the hypoxic response pathway, mediated by HIF-1 α has been associated with modulation of VEGF levels as well as other pro-angiogenic molecules such as the angiopoietins and erythropoietin²⁰. Cutaneous AS generally lacks HIF-1 α expression however²¹ and only one case report to date has documented expression of HIF-1 α in AS²². Accordingly, the hypoxic response pathway is not thought to be a significant regulator of VEGF expression in AS.

Other signaling pathways may also be important to the growth of AS. A recent tissue microarray analysis of 222 historical AS specimen describes high levels of expression of VEGF-A, -C, KIT, phospho-AKT, phospho-4eBP1 and eIF4E with significant correlative associations between KIT and p-AKT, as well as p-AKT and VEGF-A, -C, p-4eBP1 and eIF4E²³. Preclinical studies of other vascular malformations support these data^{24,25}. Notably a report of sustained endothelial cell AKT activation, in a mouse model, lead to development of tumor-associated like vessels and was reversed with rapamycin²⁶. Additionally, loss of AKT pathway regulators, such as PTEN and FoxO family members, have been associated with the development of angiosarcoma in other species^{27,28}. These data suggests that AKT signaling is likely activated in AS and in fact rapamycin has been reported to have a growth inhibitory effect on human AS cell lines *in vitro*²⁹. The p53-MDM-2 axis has also been found to be dysfunctional in AS³⁰, suggesting a role in the development of AS and potentially also an effect on growth and apoptosis control. Other series of human AS have also documented dysregulation of p53-MDM2³¹. As such, therapies interrupting this pathway are currently being explored in clinical trials.

The treatment of angiosarcoma is currently changing at a rapid pace with a transition from standard chemotherapy to molecularly targeted small molecules. Classically, systemic treatment of AS included standard chemotherapies such as the anthracycline doxorubicin or possibly ifosfamide, generate clinical responses in the range of 10-20% of patients³². Over the past decade however, the taxane family of chemotherapy has been shown to have significant anti-AS activity. This presumably owes to the anti-angiogenic effects of taxane based chemotherapy however the mechanism of this activity has not been elucidated. In an early report, a series of 9 pre-treated, advanced AS patients were treated with paclitaxel on various schedules. Of the nine, 8 major and 1 minor response were observed³³. Multiple case series and reports have detailed the activity of this agent. A retrospective review of the experience of the European Organization for Research and Treatment of Cancer (EORTC) found a response rate of 62% in 32 patients and paclitaxel was deemed to be an active agent in AS³⁴. A formal phase II clinical trial (the ANGIOTAX study) was published in 2008 detailing a progression-free survival of 74% and 24% at two and four months, respectively, with administration of weekly paclitaxel³⁵. Docetaxel, the second member of the taxane family, has also been shown to generate responses in the treatment of angiosarcoma. Six out of a total of nine AS patients treated in Japan study achieved major responses with 2 complete responses and 4 partial responses³⁶. Multiple other small series have also confirmed the activity of this agent as a single agent as well in conjunction with other chemotherapies and radiation. Pegylated-liposomal doxorubicin has also been shown recently to have anti-AS activity and is an additional effective agent³⁷.

The molecular understanding of AS has increased substantially over the past decade. As such, rationally designed drug programs have been developed utilizing the knowledge of dysregulated molecular targets such as KDR. Building on the results of these pre-clinical studies, as well as the clinical efficacy noted in a Phase I trial³⁸, a phase II trial of sorafenib, a multi-targeted tyrosine kinase inhibitor with a spectrum of activity toward VEGF, BRAF, c-KIT and PDGFR, was undertaken in soft-tissue sarcoma patients³⁹. In a sarcoma subtype specific, 6-arm phase II study, 37 patients with vascular sarcomas were evaluated noting best responses including 1 CR, 4 PRs, and response rate (RR) of 14%. Overall median progression-free survival (PFS) was 3.2 months; median overall survival (OS) was 14.3 months. Patients with angiosarcoma were noted to have the greatest degree to tumor shrinking overall of all sarcoma subtypes. Notably, no RECIST responses among the epithelioid hemangioendothelioma or hemangiopericytoma-solitary fibrous tumor patients were seen, again implying that the biology of other vascular sarcomas is distinct from AS. Imatinib mesylate, another tyrosine kinase inhibitor with spectrum of activity including ABL, c-KIT, PDGFR, among others, has also been examined in AS⁴⁰. A response rate of 12% and non-progression rate of 20% at 3 months was reported. Bevacizumab, the anti-VEGF monoclonal antibody, has been described in small series to have activity in this disease and a preliminary report of an open-label phase II study of single agent bevacizumab has reported a RR of 12% and tumor stabilization in 62% of the 29 pts enrolled to date⁴¹. Other small molecules TKIs have been described as having activity in this AS and other soft-tissue sarcomas, including sunitinib⁴² and pazopanib⁴³. The agents available to date have targeted the VEGF pathway however a newer generation of anti-angiogenic agents is close to being realized clinically⁴⁴. These target other elements of angiogenesis, including angiopoietins, placental growth factor (PGF), HGF/cMet, NOTCH and several other pathways (**Figure 1**). As such, the options for treatment of angiosarcoma appears to be expanding. Combinations of these agents, together and with chemotherapy, are yet to be thoroughly evaluated.

DERMATOFIBROSARCOA PROTUBERANS

Dermatofibrosarcoma protuberans (DFSP) is a rare dermatologic malignancy with a propensity to be locally aggressive but is metastatic in less than 5 percent of patients⁴⁵. The cell of origin remains unknown and there is no known etiologic factors have yet been identified. DFSP represents 18.4 percent of cutaneous sarcomas as identified in the SEER database of 1992 to 2004⁴⁶. It is believed that metastasis develops more commonly in DFSP harboring areas of fibrosarcoma, known as fibrosarcomatous DFSP (DFSP-FS)^{47,48}. DFSP is characterized by a specific rearrangement of chromosomes 17 and 22, which can be detected by standard cytogenetics as translocation t(17;22) or a supernumerary ring chromosome that leads to fusion of the collagen type I A1 chain (*COL1A1*) gene chain gene to platelet-derived growth factor β chain (PDGF- β) gene⁴⁹. This chromosomal translocation results in expression of a fusion protein that is processed to a mature PDGFB homodimer and exerts its pathogenic effect through autocrine and paracrine interaction with PDGFB receptor present on the cell surface of DFSP⁵⁰.

Historically, radiotherapy has been considered a treatment option for unresectable lesions or in case of margin involvement⁵¹ and reports of effective use of cytotoxic chemotherapy are anecdotal⁵². The observation that autocrine overproduction of PDGF- β is a key factor in DFSP pathogenesis led to investigation of the effects of small molecule PDGF- β inhibitors on DFSP growth. As such, imatinib was subsequently evaluated and shown to have marked anti-proliferative activity toward DFSP pre-clinical model systems⁵³. Anecdotal reports⁵⁴ then suggested activity of imatinib in patients with advanced or metastatic DFSP and eventually a formal phase II clinical trial was initiated in patients with metastatic or advanced DFSP. The Imatinib Target Exploration Consortium Study B2225 reported a 100

percent response rate in nine patients with t(17;22); whereas the one patient with DFSP lacking this translocation had no response⁵⁵. A second phase II study of DFSP patients has also been completed and results are available from a recently published pooled analysis of the two available phase II trials of imatinib in DFSP⁵⁶. These data confirmed a median time to progression (TTP) of 1.7 years and 1-year overall survival rate was 87.5%. The median OS had not been reached. Further, it appears that imatinib has activity in all DFSP (including DFSP-FS) and neither response nor progression rates vary based on treatment with either 400 mg daily or 400 mg BID of imatinib. Imatinib has also been evaluated as preoperatively therapy. In a phase II trial of 25 patients, 21 of which were found to have the COL1A1-PDGF- β gene fusion, 9 patients were noted to have a clinical response and toxicities were limited such that no surgeries were delayed⁵⁷. Given the evidence above, imatinib is now considered the primary systemic therapy for DFSP patients with inoperable or metastatic disease and can be strongly considered in the neoadjuvant setting when the surgical approach is initially difficult.

KAPOSI'S SARCOMA

Cutaneous Kaposi's Sarcoma (KS) is a lesion of the dermis composed of aberrant vascular structures lined by abnormal-appearing, spindle-shaped endothelial cells and with extravasated erythrocytes and lymphocytes within the structure. The KS cell is believed to be of mesenchymal, endothelial origin expressing CD31, CD34, and EN4. These tumors generally appear as flat or raised lesions and progress to plaque-like or nodular lesions. Bacillary angiomatosis may be confused with the initial presentation of KS lesions. KS remains one of the most common AIDS-related malignancies and transplant-related malignancies in the United States⁵⁸⁻⁶⁰.

There are four forms of KS, including classic KS, endemic KS, transplant-associated KS and AIDS-associated or epidemic KS. KS lesions are often associated with lymphedema and an angiogenetic stimulus is thought to be elicited by the disruption of lymphatic channels. Both the disruption of lymph channels and the associated angiogenesis are thought to contribute to an environment conducive to vascular tumor formation⁶¹. All four forms of KS present with identical histologic appearance, suggesting a similar etiologic agent and pathogenic mechanism⁶². Chang et al. identified a viral cause of KS in a patient with AIDS and KS⁶³. This KS-associated herpesvirus, Human herpes virus-8 (HHV8), is present in greater than 90 percent of AIDS-related tumors, as well as classic KS, post-transplant-related KS and endemic African KS⁶². In the case of AIDS-associated KS, correlation between viral antibody titers as well as viral load have been correlated with early signs of KS development^{64,65} and overall disease course⁶⁶, respectively.

Treatment options for individual KS lesions include topical retinoic acid, cryotherapy and local irradiation. The treatment of AIDS-associated KS generally requires an individual approach based on several factors including goals of care, such as palliation of symptoms, alleviation of edema, cosmetic considerations and others, as well as other factors such as extent of disease, viral load/CD4 count and rate of tumor progression, among others⁶⁷. In all AIDS-associated KS patients however, it is essential to optimize control of HIV infection. The institution of highly active antiretroviral therapy (HAART) has markedly reduced the number of new cases of KS diagnosed⁶⁸ and there is suggestion that HAART has changed the natural history of KS⁶⁹. Reconstitution of the immune system is presumed to be the mechanism underlying this with evidence of support including increased incidence of Immune Reconstitution Syndrome (IRIS) in KS patients⁷⁰. While several strategies are common in direct local treatment of KS lesions, restoration of immune competence with HAART is now standard of care in AIDS-associated KS. Complete discussion regarding the idiosyncrasies of anti-viral directed therapy is beyond the scope of this review. It should be

understood however, that several approaches of therapy against HIV and/or HHV8, with both standard antibiotic approaches, such as variations on HAART and ganciclovir, as well as epigenetic anti-viral approaches, with histone deacetylase inhibitors (HDAC), are the subject of ongoing investigations.

Systemic anti-neoplastic therapy is generally warranted for KS patients with more advanced cutaneous disease or lesions refractory to topical or localized treatments. Four agents are currently approved for systemic treatment of KS including liposomal anthracyclines (including daunorubicin and doxorubicin), paclitaxel, and interferon- α (IFN- α)⁷¹. Several other agents, including bleomycin, the Vinca alkaloids (vinblastine, vincristine, vinorelbine) and etoposide have also been described to have activity in this disease⁷². Historically, systemic treatment regimens relied on combination therapies with considerable treatment-related toxicities. More recently, the importance of palliation has come more forefront as more active agents, such as the liposomal anthracyclines, have demonstrated single agent efficacy in all forms of KS⁷³. Liposomal anthracyclines are now considered standard of care first line therapy in KS based on multiple clinical trials establishing equivalent or improvement in efficacy as compared to older chemotherapy regimens such as doxorubicin, bleomycin and vincristine (ABV)^{74,75} or bleomycin and vincristine (BV)⁷⁶. Additionally, the toxicity profile associated with these agents has been improved markedly as compared to the first generation of anthracyclines, now with limited cardiotoxicity and other side effects such as fatigue and nausea. Paclitaxel is generally reserved for second line therapy, as this agent has been shown to have significant anti-tumor effect even in liposomal anthracycline failures⁷⁷, however a recently reported phase II trial has also confirmed equivalent efficacy in the front line setting when compared to liposomal doxorubicin⁷⁸. IFN- α is also FDA approved for treatment of KS however the clinical response rate is somewhat lower than that seen with standard cytotoxic agents and the benefit of this therapy appears to be greatest in patients with predominately skin based disease and less severe immunosuppression^{79,80}. This is improved with the use of high-dose IFN- α , however such administration must be considered within the context of the known significant toxicity profile (fevers, chills, rigors, depression, cognitive impairment, neutropenia, hepatotoxicity, etc.) associated with IFN- α administration.

Beyond standard cytotoxic agents and IFN- α however, recent advances in the molecular understanding of KS have led to interest in the development of small molecules and further immunotherapies in the treatment of KS. The AIDS Malignancy Consortium (AMC) has been instrumental in evaluating these treatments and the AMC continues to facilitate the advancement of the field in KS treatment. **Figure 2** lists the clinical trials currently being administered by the AMC.

Molecular targets in KS vary widely and include classic pathway inhibition strategies (blockade of RTKs or downstream effectors), further immunotherapy treatments, as well as anti-angiogenesis agents. Of these, the closest to standard clinical use include tyrosine kinase inhibitors, such as imatinib, and other small molecules inhibiting the AKT/mTOR pathways. As with several other sarcoma sub-types, multiple RTKs including KIT, PDGFRA and insulin-like growth factor receptor (IGFR), have been identified as important in the growth of KS cells⁸¹. Preclinical studies have established that inhibition of surface receptors with small molecules can retard growth of KS cells in culture, including those overexpressing multi-drug resistance mechanisms⁸². These observations have been taken forward into small pilot studies including a series of ten AIDS-associated KS patients who were treated with imatinib⁸³. Five of the ten had objective clinical responses to treatment. Four of six patients who had pre-treatment and post-treatment biopsies had evidence of PDGFR target inhibition. Sorafenib has also been described to have anti-tumor activity in KS⁸⁴, however the mechanism of action may differ from imatinib in that sorafenib inhibits

VEGFR in addition to PDGFR. Similarly, signaling through the AKT/mTOR pathways, which are downstream of the constitutively active HHV8 viral G protein-coupled receptor, vGPCR, has been observed to be important in Kaposi sarcomagenesis as well as in maintenance of the malignant phenotype^{85,86}. As with TKI studies, inhibitors of these pathways have been observed to marked anti-tumor effect both *in vitro*⁸⁷ and an increasing body of clinical observations has noted rapid resolution of both cutaneous and visceral Kaposi's lesions in response to transition from other immunosuppressive strategies to rapamycin analogs (mTOR inhibitors) in both the renal⁸⁸ and cardiac transplant settings⁸⁹. Preliminary case series have described responses of KS to these agents in human subjects⁹⁰ however robust clinical data is still pending to date. Inhibition of the NF- κ B pathway has also generated excitement as a potential therapeutic tool in KS. Upregulation of NF- κ B activity is mediated by a viral oncoprotein known as vFLIP, which eventually leads to dysregulation of TRAIL associated, caspase-mediated apoptosis⁹¹. Bortezomib, a broadly active proteasome inhibitor, is known to inhibit the NF- κ B pathway and as such is currently being evaluated in clinical trials of KS patients. Taken together these observations suggest a slow shift in the overall paradigm in the systemic treatment of KS from that of non-specific cytotoxic chemotherapy to rationally tailored small molecule strategies.

Immunotherapy also continues to be of interest in addressing KS. Specifically, the cytokine IL-12 has been proposed to have potential clinical benefit in this disease. IL-12 is known to be a regulator of type 1 immunity, inducing production of interferon- γ (IFN- γ), and mediating antiangiogenic effects⁹². Further, IL-12 appears to have a direct downregulation activity of vGPCR⁹³. The activity of IL-12 was initially established in a phase I trial of AIDS-associated KS patients⁹⁴. In 32 total patients, 17 of 24 patients treated at doses greater than 100 ng/kg had objective clinical responses. This agent was subsequently evaluated in a phase II combination with liposomal doxorubicin with impressive results⁹⁵. Thirty out of 36 patients were seen to have a response with nine complete responses. Given these results, it appears that while active as a single agent, IL-12 activity appears to be enhanced when combined with cytotoxic therapy. Again, side effects of immune based therapy must be considered closely when such a strategy is employed however the potential for complete resolution of malignancy supports the rationale immunotherapy as a treatment paradigm.

Similar to angiosarcoma, KS is a disease driven by aberrant blood vessel formation and growth. As such, targeting the angiogenesis process is a rational approach. It is now clear that aberrant endothelial growth in KS is driven by vGPCR through activation of hypoxia inducible factor 1- α (HIF1 α), and other viral encoded proteins, eventual leading to upregulation of VEGF⁹⁶. Given this, multiple therapies targeting the VEGF pathway, including bevacizumab, other anti-VEGFR directed TKIs and the novel VEGF post-transcriptional inhibitor (PTC-299) are being evaluated.. Other angiogenesis targets are also of interest. The extracellular matrix, matrix metalloproteinases specifically, have been shown to contribute to neoplastic angiogenesis through disruption of the basement membrane and other structures⁹⁷. In KS, this has been further characterized to be driven through glycoproteins such as emmprin⁹⁸. Early phase trials are assessing the inhibition of MMPs⁹⁹⁻¹⁰² however further development is required prior to clinical realization of these strategies. Non-specific inhibitors of angiogenesis, including agents such as fumagillin and thalidomide, have been documented to have activity in small case series and early phase trials¹⁰³⁻¹⁰⁵. Similar to anti-MMP directed therapy, these modalities will require further clinical development before becoming more broadly applicable to KS patients. As described above for angiosarcoma, as the significance of other angiogenesis pathways, such as PGF, angiopoietins, NOTCH and others, become further elucidated in KS, inhibitors of these will likely have bearing on the treatment of KS patients.

CUTANEOUS LEIOMYSARCOMA

Cutaneous Leiomyosarcoma (LMS) are rare tumors generally arising on the thorax or extremities and involving both the cutaneous or subcutaneous layers. The incidence of these tumors is low and the patient population most often affected is those in the sixth decade of life¹⁰⁶. These lesions present as intracutaneous or subcutaneous nodularity with a violaceous vascular phenotype that can be asymptomatic or painful¹⁰⁷. Histologically, these lesions appear to be composed of spindle-shaped cells arranged in longitudinal fascicles with cytologic atypia consistent with differentiation toward arrector pili or vascular smooth muscle¹⁰⁸. The diagnosis of primary LMS of the skin is difficult often leading to inconsistency in diagnosis. Immunohistochemical markers are not well standardized however all case series to date have described positive staining for smooth muscle actin and a majority of cases stain for desmin¹⁰⁹. Purely cutaneous LMS are known to be locally recurrent following resection however the metastatic potential of these lesions is essentially nil. LMS involving the subcutaneous skin layers however is known to have metastatic potential and more aggressive clinical course^{110,111}.

Resection of primary treatment of cutaneous LMS is associated with a high cure rate^{106,112}. Consolidative radiotherapy has also been associated with an increased chance for cure in some series¹¹³ and chemotherapy is often considered if the resected lesion is found to have a high histological grade¹¹⁴. Additionally, most series have described the use of chemotherapy upon progression to metastatic disease. Treatment agents in both the adjuvant and metastatic setting have varied however generally include those agents classically associated with sarcoma treatment including doxorubicin, ifosfamide, gemcitabine and docetaxel and dacarbazine.¹¹⁵ Approximately 100 cases of cutaneous LMS have been described in the literature to date, and limits the interpretation of effective approaches to treatment of recurrent or unresectable disease.¹¹⁶

Given the rarity of this in diagnosis, advances in the treatment of cutaneous LMS generally should be considered in the context of LMS of soft tissue. The combination of gemcitabine and docetaxel in treatment of metastatic LMS is the only regimen to document an overall survival (OS) benefit in STS^{117,118}.

Similar to the other tumors described above, the molecular understanding of LMS is advancing and new neoplastic targets are being identified.. LMS has been shown to overexpress several RTK families including IGFR, c-KIT, PDGFR and likely others¹¹⁹⁻¹²². A phase II study of imatinib in 10 different sarcoma sub-types, including LMS, documented at least stable disease in all sub-types; preliminarily implying a role for KIT or PDGFR targeting in this disease¹²³. Additionally, LMS, and cutaneous LMS especially, seems likely to be sensitive to inhibition of the VEGFR pathway given the vascular phenotype observed and the observation that of all soft tissue sarcomas, LMS is one of the most likely to overexpress VEGFR¹²⁴. Trials to date of small molecules potentially targeting VEGFR have been mixed. A phase II study of sunitinib in 2nd or 3rd line uterine leiomyosarcoma revealed a response rate of only 8.7% and was not considered a useful agent in this population¹²⁵ however a phase II study of pazopanib, a TKI with spectrum of activity including VEGFR, PDGFR and KIT, in advanced high-grade STS, documented an improvement of progression free rate at 12 weeks in LMS patients of 44%⁴³. As such, further development of this agent, in this disease, is planned.

CONCLUSION

Cutaneous sarcomas are rare tumors that often pose a difficult diagnostic delima and require a multi-disciplinary approach for appropriate management. Surgical resection remains the

gold standard treatment of cutaneous sarcomas. While systemic therapy options for advanced cutaneous soft-tissue sarcomas remain limited a number of novel and targeted therapies are under investigation for patients with recurrent or unresectable disease. With the advent of more effective targeted therapies, preoperative management of marginally resectable or recurrent cutaneous disease will likely have a greater role. Given the rarity of refractory cutaneous sarcomas, the evaluation of these novel treatments will likely be conducted in the setting of more common soft-tissue sarcomas and require the cooperation of investigators in order to move the field of targeted therapeutics forward. The use of biologic correlates in trial design will complement and facilitate the evaluation of new treatment efficacy and serve as a platform for the next generation of further studies and further potential drug targets.

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