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REVIEW

Epidemiology and therapies for metastatic sarcoma

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Abstract: Sarcomas are cancers arising from the mesenchymal layer that affect children, adolescents, young adults, and adults. Although most sarcomas are localized, many display a remarkable predilection for metastasis to the lungs, liver, bones, subcutaneous tissue, and lymph nodes. Additionally, many sarcoma patients presenting initially with localized disease may relapse at metastatic sites. While localized sarcomas can often be cured through surgery and often radiation, controversies exist over optimal management of patients with metastatic sarcoma. Combinations of chemotherapy are the most effective in many settings, and many promising new agents are under active investigation or are being explored in preclinical models. Metastatic sarcomas are excellent candidates for novel approaches with additional agents as they have demonstrated chemosensitivity and affect a portion of the population that is motivated toward curative therapy. In this paper, we provide an overview on the common sarcomas of childhood (rhabdomyosarcoma), adolescence, and young adults (osteosarcoma, Ewing sarcoma, synovial sarcoma, and malignant peripheral nerve sheath tumor) and older adults (leiomyosarcoma, liposarcoma, and undifferentiated high grade sarcoma) in terms of the epidemiology, current therapy, promising therapeutic directions and outcome with a focus on metastatic disease. Potential advances in terms of promising therapy and biologic insights may lead to more effective and safer therapies; however, more clinical trials and research are needed for patients with metastatic sarcoma.

Keywords: chemotherapy, pediatric sarcoma, rhabdomyosarcoma, osteosarcoma, Ewing sarcoma, synovial sarcoma

Introduction

Sarcomas, cancers of tissues derived from the mesenchymal layer, represent 1% of all cancers in adults, 10% of cancers in children, and 8% of cancer in adolescents and young adults. This rarity and the diversity across ages render diagnosis and treatment difficult. In 2012, 2890 new cases of bone and joint cancer and 11,280 new cases of soft tissue cancer were estimated in the USA.[1] In this same year, 1410 and 3900 deaths due to bone and soft tissue cancers, respectively, were also estimated. Despite being rare, sarcomas contribute to a substantial loss of years of life compared to other cancers because of the many children, adolescents, and young adults diagnosed with sarcoma.

Sarcomas are broadly classified as either soft tissue or bone neoplasms. There is substantial diversity in the more than 50 histologic soft tissue sarcoma (STS) subtypes.[2] Peak incidence differs according to the histologic subtype with rhabdomyosarcoma being the most common type in early childhood, bone sarcomas predominating in

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adolescence, and multiple histologic types of soft tissue sarcomas predominating in young adulthood (<40 year old) and in older adults. From 2005–2009 approximately 29% of bone and joint cancer cases were diagnosed in patients under 20 years and 15% were diagnosed in 20–34 year olds. Nine percent of soft tissue cancer cases were diagnosed at <20 years or 20–34 years.[3]

At present, it should be noted that metastatic sarcomas are defined by the presence of disease to any metastatic site. This definition of metastasis may change over time with the advent of more sensitive measures for detecting metastatic disease. Currently, micrometastases are frequently below the detection limit of modern scans. Perhaps biomarkers such as circulating tumor cells, tumor-specific DNA markers such as translocations, tumor-specific antigens, or microRNAs (miRNAs) may eventually be incorporated into the definition of metastases.[4–9]

In this report, we will review the epidemiology, current therapy and promising therapeutic directions, and outcomes of patients with metastatic sarcoma. This review will include the common sarcomas of childhood (rhabdomyosarcoma), adolescence and young adults (osteosarcoma, Ewing sarcoma, synovial sarcoma, and malignant peripheral nerve sheath tumor), and older adults (leiomyosarcoma, liposarcoma, and undifferentiated sarcoma). We will also discuss patients who present with localized disease but unfortunately relapse at metastatic sites.

Epidemiology

Incidence and survival

Incidence and survival statistics were obtained from Surveillance, Epidemiology, and End Results (SEER) Fast Stats, an interactive tool that allows access to SEER and US cancer statistics.[10] In 2009, STS accounted for 85.6% of all sarcomas diagnosed in the USA, whereas bone and joint sarcoma accounted for 14.4%. The incidence of STS is highest in individuals aged 65+ years and lowest in those <20 years (Figure 1). The 10-year relative survival rate for STS among patients < 20 years old was 70%, but approximately 50% among patients > 65 years old (Figure 2). The incidence of bone and joint cancer is highest in individuals aged 65+ years and lowest in those aged 20–49 years (Figure 3). The 10-year relative survival rate for patients diagnosed at 20–49 years with bone and joint sarcoma is 70% and about 40% for patients diagnosed > 65 years (Figure 4). SEER does not distinguish between metastatic and lower stage sarcomas and, as detailed throughout this report, patients with metastatic sarcoma have a worse prognosis than those listed in the figures.

Risk factors

Sarcoma most typically presents spontaneously without a demonstrable cause. However, several risk factors have been associated with its development, including exposure to radiation and chemotherapeutic agents, viral infections, occupational factors, hereditary syndromes, certain diseases, and hormones.

Radiation and chemotherapeutic agents

Ionizing radiation has been consistently reported to be associated with increased risk of bone and STS of up to 1%. In children, studies have shown increased risk after high-dose fractionated radiation exposure (>10 Gy), which increases approximately linearly in dose until about 40+ Gy.[11]

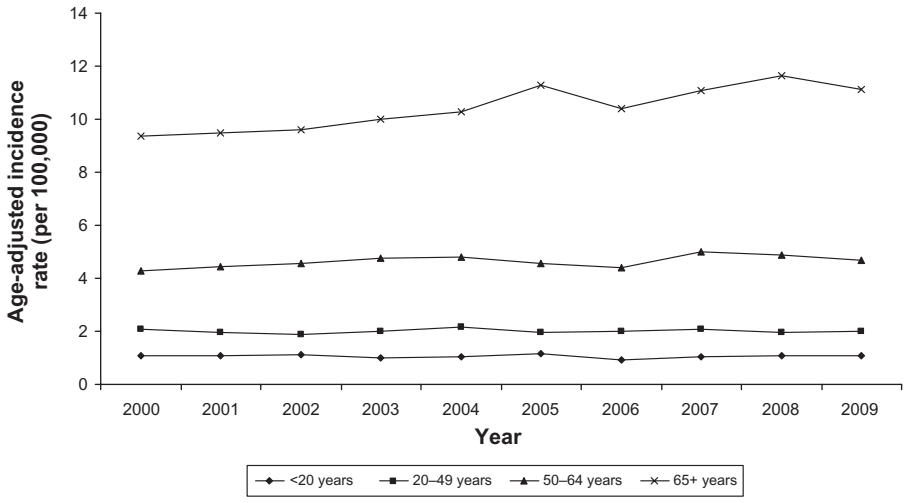

Figure 1 Age-adjusted incidence rates of soft tissue sarcoma by age at diagnosis (SEER18 areas).
Abbreviation: SEER, Surveillance, Epidemiology, and End Results.

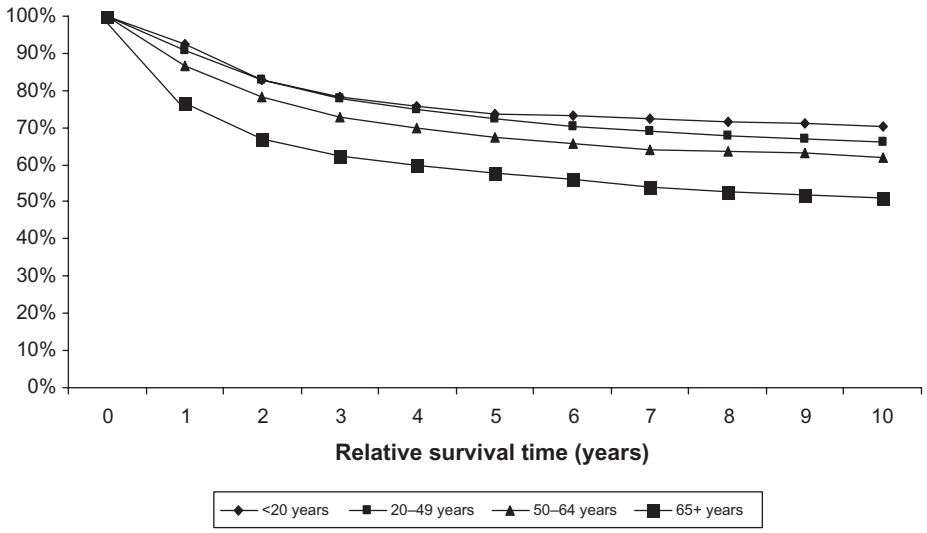

Figure 2 Relative survival of soft tissue sarcoma for different age groups, 1988–2008 (SEER 9 areas).
Abbreviation: SEER, Surveillance, Epidemiology, and End Results.

Interestingly, this risk declines after 40+ Gy, possibly due to high levels of cell killing, which may include precursors of sarcoma.[12] These findings are controversial as the majority of the study participants had retinoblastoma, a condition that increases the risk for sarcoma development. Regarding radiotherapy, limited data have suggested an increased risk after high-dose exposure in adult sarcoma patients.[11] In a study of 100,000 women with breast cancer in Sweden, dose of radiotherapy predicted sarcoma development, except angiosarcoma.[13] In addition, recent findings from studies on Japanese atomic bomb survivors have suggested that the risk of sarcomas is elevated by acute lower doses of radiation (<5 Gy) at any age.[11] Osteosarcoma is the most common type of post-radiation sarcoma, followed by malignant fibrous histiocytoma and fibrosarcoma.[14] The good absorption of radiation by bone may account for the high incidence of bone sarcoma relative to other sites.

In addition to radiation, alkylating agents such as cyclophosphamide have been reported to be an independent risk factor for bone sarcoma. Tamoxifen, a commonly used agent for the treatment of estrogen receptor-positive breast cancer, has been linked to the development of uterine sarcomas.[15]

Viral infection

Epstein–Barr virus (EBV) and Kaposi's sarcoma-associated herpes virus (KSHV), also known as human herpes virus 8 (HHV-8), play direct roles in carcinogenesis-encoding

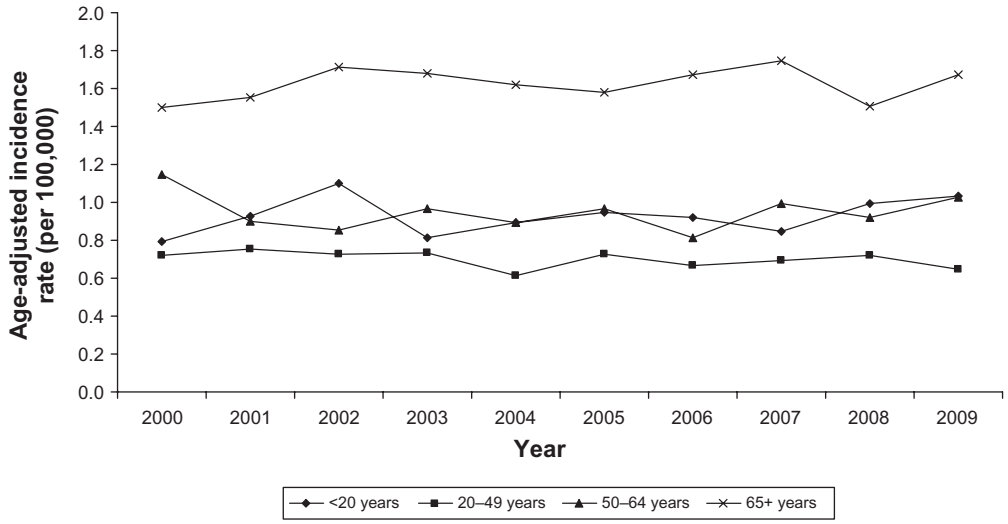

Figure 3 Age-adjusted incidence rates of bone and joint cancer for different ages at diagnosis (SEER 18 areas).
Abbreviation: SEER, Surveillance, Epidemiology, and End Results.

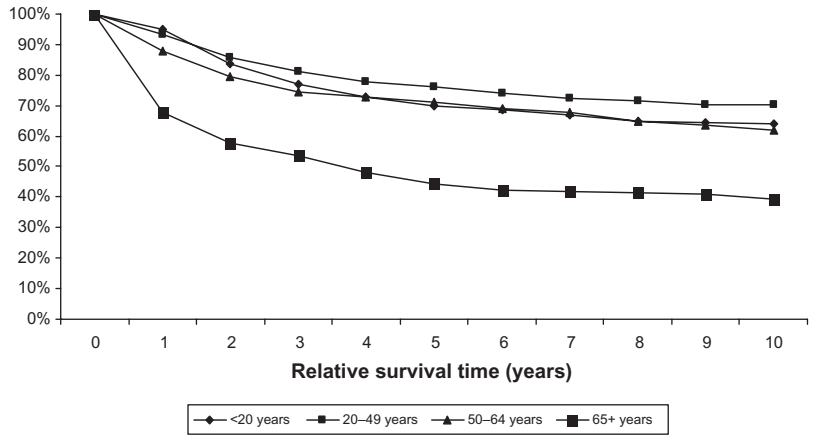

Figure 4 Relative survival of bone and joint cancer for different age groups, 1988–2008 (SEER 9 areas).
Abbreviation: SEER, Surveillance, Epidemiology, and End Results.

oncoproteins that are able to promote cellular transformation. Both of these human gamma herpes viruses are known for their oncogenic properties, for the viral products that mimic or interfere with the functions of critical cellular proteins, and for their ability to escape immune responses.[16] Greater than 90% of the world population is infected with EBV, and EBV has been implicated in the development of leiomyosarcomas in HIV-infected and transplant patients.[17] Associations between EBV and HHV-8 have been noted to occur in the setting of chronic immunosuppression (ie, untreated HIV patients or patients with a history of organ transplantation).

Occupational factors

Associations between job type and sarcoma risk have been reported, but with inconsistent results. For example, the association between agriculture-based occupations and risk of sarcoma has been positive in some analyses and negative in others.[18–20] These inconsistencies may potentially be due to the small number of cases in some of the studies. Other occupations, such as blacksmiths, toolmakers, machine-tool operators, carpenters, health-related occupations (such as radiologists), and individuals working in the manufacturing of wood, cork products, and straw, have been reported to have an increased risk for bone tumor.[21,22] Exposures to several chemical agents, including dioxin, chlorophenols, and other solvents have also been associated with the risk of STS development;[23–25] other studies did not observe these associations, however.[26–28]

Hereditary syndromes

The risk of sarcoma increases with different inherited genetic syndromes, including Li–Fraumeni syndrome, retinoblastoma, Werner's syndrome, Rothmund-Thompson syndrome, neurofibromatosis, and enchondromatosis. Li–Fraumeni syndrome results from germline mutations in the *TP53* suppressor gene. Sarcoma patients are more likely to have *TP53* germline mutations, and sarcoma represents 25% of tumors in *TP53* mutation carriers.[29] Retinoblastoma develops through germline mutations in the *RB1* tumor suppressor gene, and retinoblastoma survivors have shown an increased risk of sarcoma compared to the general population.[30] Werner syndrome is an autosomal inherited disease caused by a mutation in the DNA helicase gene, *WRN*. Werner syndrome patients have an increased propensity to develop sarcomas[31]. Neurofibromatosis patients have a 10% cumulative lifetime risk of developing sarcoma.

Disease

Paget's disease of bone is a focal disorder of bone metabolism mediated by abnormal osteoclast function. This disease has been associated with about 1% of osteosarcomas. These cancers occur mostly in patients with long-standing polyostotic disease who are older than 65 years of age.[32,33] A molecular basis for the association of osteosarcoma with Paget's disease is unclear.

Diamond Black fan anemia is an inherited red blood disorder where 40% of patients have mutations in genes important in ribosomal function.[34] This condition is associated with an increased risk of osteosarcoma,[35] suggesting a potential role of ribosomal proteins in osteosarcoma development, although data in this area are very limited.

Hormones

The differential incidence of histologic subtype-specific sarcomas between the genders has suggested that hormones may be involved in tumorigenesis of sarcoma, including

leiomyosarcoma, but data on their potential role are limited. In a case control study of 104 STS patients and 505 controls, no significant associations between female hormone-related factors, including parity, age at menopause, and menstrual cycle patterns, were shown.[36] However, a suggestive association was observed in women who were first pregnant at age > 29 years. In addition, use of oral contraceptives has been reported to increase the risk of chondrosarcoma.[37]

Other risk factors

Various studies have reported on other risk factors associated with the development of sarcoma in children, including the use of antibiotics[38] or medications for vomiting and nausea during pregnancy[39] or the use of antibiotics in children soon after birth. Some studies have suggested an association between pediatric sarcoma and birth weight,[40] gestational age,[41] birth order and maternal age,[42,43] and occupation.[21] However, results have been inconsistent, and further studies are needed to confirm these observations. Available data on height suggest that taller individuals are more likely to develop osteosarcoma.[40] Additional information on the epidemiology of sarcoma has been summarized nicely in a recent review article.[44]

Rhabdomyosarcoma

Rhabdomyosarcoma, a malignancy of primitive muscle, predominates in pediatric patients but can be seen at any age.[45,46] In 2009, rhabdomyosarcomas comprised 3.2% of STS diagnosed in the USA. It typically presents as a painless mass that interferes with organ function, with symptoms depending on location. There are multiple histologic subtypes, with the alveolar and embryonal subtypes being the most common forms in childhood.[45] Many clinical features contribute to rhabdomyosarcoma staging and risk grouping, including tumor size, location of primary tumor, degree of surgical resection, histologic subtype, and presence of nodal or metastatic disease.

Current therapy

Roughly 16% of newly diagnosed rhabdomyosarcoma patients have metastatic disease.[47–49] The most common metastatic sites include lung (18%–39%), lymph node (30%–49%), bone marrow (32%–37%), and bone (27%–33%).[50–52] Chemotherapy is standard for all pediatric high-risk and relapsed patients. Surgery, radiation, or a combination is employed for local control of primary tumors. Patients with lymph node-only metastases and the alveolar subtype have a prognosis similar to patients with hematogenous metastasis. On the other hand, embryonal rhabdomyosarcoma patients who are young (<10 years old) with lymph node-only metastasis have a prognosis similar to patients with localized disease.[53] Patients with metastases are more likely to be older, have alveolar subtype, have larger primary tumors, and present with an extremity or other unfavorable site primary tumor.[51,52] Although outcomes have been stagnant over many years, a recently completed clinical trial (ARST0431) demonstrated improved short-term survival, especially for those with embryonal rhabdomyosarcoma, using a combination of past-tested agents, including vincristine, dactinomycin, cyclophosphamide, ifosfamide, etoposide, doxorubicin, and irinotecan; follow-up for this regimen is ongoing.[54]

Emerging therapies

Another ongoing study, through the Children's Oncology Group (COG), has added an insulin growth factor receptor 1 antibody (IMC-A12) to the ARST0431 regimen (National Clinical Trial [NCT] #01055314), with aims of improving early disease control and determining the feasibility of the chemotherapy combination with biologic correlates. Bevacizumab and temsirolimus are also being evaluated in relapsed and refractory patients in a randomized fashion when added to vinorelbine and cyclophosphamide to estimate and compare event-free survival between groups (NCT#01222715). The role of higher dose chemotherapy with stem cell rescue has thus far not been validated.[55,56] The pleomorphic and undifferentiated histologic subtypes of rhabdomyosarcoma, which are more common in older adults, are more resistant to chemotherapy and may present more commonly with metastatic disease. These are not treated the same as childhood rhabdomyosarcoma and are included in the leiomyosarcoma section.

Osteosarcoma

Osteosarcoma is the most common bone sarcoma in children and adolescents. Osteosarcoma accounts for approximately 400 new cancer diagnoses per year in children less than 18 years old and for a total of about 1000 new diagnoses per year. Although it affects all ages, the clear peak incidence is the period of puberty and adolescence followed by another peak in the 7th decade,[34] with the majority of cases in the adult population. However, more is known about pediatric osteosarcoma through carefully conducted, randomized, single institution, and cooperative group trials.[57] When treated by surgical resection alone, only 16% of patients have long-term survival, suggesting that micrometastasis is present in an overwhelming majority of newly diagnosed patients.[58,59]

In a large collaborative pediatric series, osteosarcoma presented with detectable metastatic disease in 11% of patients.[60] The importance of complete surgical resection, burden, and location of disease for the prognosis of metastatic patients has been established.[61]

Metastatic osteosarcoma at diagnosis and relapsed disease with metastases both portend a poor prognosis. With primarily diagnosed metastatic osteosarcoma, metastasis location and burden correlate with outcome, with unresectable disease generally being incurable. Patients with multifocal bone osteosarcoma have high rates of Li–Fraumeni syndrome.[62]

Current therapy

Osteosarcomas require surgical control for cure, but a clear benefit of cytotoxic chemotherapy was established in the early 1980s. Patients with metastatic and unresectable disease have a dismal prognosis with very few long-term survivors. Additional agents such as MTP-PE (muramyl tripeptide phosphatidylethanolamine) have not improved cure rates in patients with osteosarcoma.[63,64] In adolescent and young adult patients aged 18–40, less information is known, and very little has been reported in metastatic patients over 40. One report of young adults enrolled in cooperative group studies shows an inferior outcome for young adults due to increased distant relapse.[65] Retrospective reports differ regarding the outcome of older patients versus pediatric patients.[66,67] Improving outcomes was the aim of two recent COG studies: one studied the addition of trastuzumab and the other studied the addition of zoledronic acid to a chemotherapeutic backbone of doxorubicin, cisplatin, high-dose methotrexate, ifosfamide, and etoposide. Although trastuzumab plus doxorubicin was tolerated with acceptable cardiotoxicity, no clear overall benefit was shown, including in patients with high Human Epidermal Growth Factor Receptor 2 (HER2) levels by immunohistochemistry.[68] It is too early for results on the zoledronic acid study.

Roughly 30% of localized osteosarcoma patients and 80% of patients presenting with metastatic disease will ultimately relapse.[69] Many reviews have evaluated prognostic factors for distant relapsed patients. Relapses are frequently in the lung (60%–85% of patients), are local (10%–20%), or in bone (10%–20%).[70,71] In the largest reported series (576 patients) median time from diagnosis to relapse was 1.6 years, with 469 patients (81%) with lung metastasis and 90 (16%) with bone metastases.[70] Metastasectomy is clearly necessary for long-term disease-free interval or for potential cure, as there were no 5-year survivors in the unresected group (229 patients), whereas resected patients had a 5-year survival of 39%.[70] Long interval to relapse, single site or side of pulmonary metastasis, and use of chemotherapy were among the positive prognostic variables.[70] Short time to progression to lung metastases, central location, increased number of lesions, and bilateral disease are adverse prognostic factors, and patients with bilateral relapse have almost universally poor outcomes.[72] Second and beyond relapses are very likely to be pulmonary and have a poor overall outcome.[73] Bone metastatic disease either synchronous or metachronous is associated with a very poor but not uniformly fatal prognosis and, similar to patients with local and lung metastatic disease, requires surgery for a chance of cure.[62,70,74]

Emerging therapies

Two of the most well studied cell-cycle related tumor suppressors are RB1 and p53. The genes, or their pathways are mutated in the majority of osteosarcomas, but targeting these aberrations has proved to be difficult.[33,75] No other clear, recurrent, genetic changes have thus far been observed in osteosarcoma, although putative genes and pathways have been explored, including HER2.[68] An evaluation of 98 models or tumor samples of osteosarcoma showed very few point mutations of oncogenes and tumor suppressor genes commonly mutated in carcinomas; the PI3K pathway did emerge as a recurrently disrupted pathway in a subset of the patients.[76] Emerging deep sequencing data have supported the idea that a process known as chromothripsis may be important in osteosarcoma development.[77] This process involves numerous translocations acquired as a single event from chromosome shattering and re-annealing. A potential therapeutic target has thus emerged, with microtubule inhibitors demonstrating preclinical activity in osteosarcoma models.[78]

There are two ongoing studies in patients with relapsed metastatic osteosarcoma to lung: one with inhaled liposomal cisplatin (NCT01650090) and another with the SRC inhibitor saracatinib in the adjuvant setting following lung only recurrence (NCT00752206). Other compounds that may be translated into upcoming trials include mammalian target of rapamycin (mTOR) inhibitors, PI3K pathway inhibitors, anti-microtubular agents, cell cycle protein inhibitors, disruptors of osteoclast activity (receptor activator of nuclear factor-κB ligand inhibitors and bisphosphonates), immune strategies, and other targeted agents.

Ewing sarcoma

There are roughly 250 new cases of Ewing sarcoma per year in the USA, with 20%–30% of these patients presenting with metastases.[79] More than 90% of patients

display rearrangement of the *EWS* gene, most often to *FLI1*. Although results are mixed, in general, adult patients have a poorer prognosis than children and adolescents. It has long been known that metastasis is the poorest clinical prognostic marker for patients with Ewing sarcoma;[80] however, there have been improvements in survival for both localized and metastatic patients over time.[81]

Current therapy

Patients with metastatic or unresectable Ewing sarcoma have a dismal prognosis, especially those with a large metastatic tumor burden or bone marrow disease. Vincristine, doxorubicin, and cyclophosphamide, alone or alternating with ifosfamide and etoposide, are typically used for patients with metastatic Ewing sarcoma. Metastatic presentation is most often in the lungs, although it can occur in bones, bone marrow, and other soft tissues.[82] Unfortunately, systemic chemotherapy trials have not been able to improve dramatically upon the durable remission rates for patients with metastatic Ewing sarcoma. Patients without marrow disease may benefit from intensive chemotherapy followed by autologous hematologic stem cell rescue, but new strategies are actively sought in patients with metastatic disease, including targeted agents.[82] An example includes the addition of agents targeted to the insulin growth factor receptor though support for these agents for a rare disease is waning among drug companies.

Emerging therapies

Although the pathophysiology of Ewing sarcoma is thought to be tightly related to transcriptional alterations in the context of the t(11;22) EWS/FLI1 translocation, therapies related to this altered fusion protein have not yet been incorporated into practice. There has been a steady identification of biological targets in Ewing sarcoma over the past few years, including clinical trials focused on the insulin growth actor receptor 1 (IGFR-1), a receptor tyrosine kinase overexpressed in Ewing sarcoma cells. Several trials completed in unselected populations of Ewing sarcoma patients have unfortunately not shown these dramatic responses (temporary responses limited to 5%–15% of patients on the order of a few months).[83–88] Although this strategy is still being explored in the metastatic setting, IGFR-1 inhibition in patients with localized disease has lost the support of the drug industry, and to date no salient predictive biomarker has been identified. Another recent strategy, which added an mTOR inhibitor (temsirolimus) to further downregulate the pathway, was attempted with IGFR-1 immunohistochemistry (IHC) used to stratify patients in all sarcomas, including those with Ewing sarcoma. Overall, there was no clear predictive value to IGFR-1 IHC for response (personal communication).

Other promising therapeutic strategies include poly(ADP-ribose) polymerase (PARP) inhibitors, mithramycin, and a small molecule inhibitor of a protein–protein interaction, which includes EWS/FLI1. Although elevated levels of PARP in Ewing sarcoma cells were noted 20 years ago, only recently has this strategy attracted strong interest.[89,90] An ongoing trial is investigating what proportion of unselected Ewing sarcoma patients would benefit from this strategy (NCT01583543).

Two other small molecules are being explored with a mechanism of action of disrupting the translocation protein itself. Mithramycin (ongoing study NCT01610570) is an older antibiotic identified in a drug screen, and YK-4-279 disrupts the EWS/FLI1 interaction with a binding partner, RNA helicase A.[91–96] Presumably, these agents would not face the same barriers that PARP inhibitors or the IGFR-1 antibody have faced, as the fusion transcript is thought to be more central to the pathophysiology of Ewing sarcoma.

Soft tissue sarcomas

Soft tissue sarcomas most often present as a painless mass and the diagnosis is made by a combination of history and physical exam, radiologic features, and tissue biopsy. Most STS are localized, and histologic grade, tumor size, patient age, and tumor subtype are the major determinants of the therapeutic approach. Many STS display a remarkable predilection for metastasizing through circulation to the lungs. Other sites of metastasis include, but are not limited to, the liver, bones, and subcutaneous tissue with wide variation in the likelihood of metastasis to these areas depending on subtype. A minority of subtypes (synovial sarcoma, rhabdomyosarcoma, epithelioid sarcoma, clear cell sarcoma, and angiosarcoma) may metastasize to lymph nodes and, even more rarely, to other sites of the body.[97,98] Histologic grade is an independent predictor of metastasis development for the main histologic types of adult STS.[99]

Adolescent and young adults (AYA) (18–40 years old) typically fare worse than both the younger and older cohorts of patients for a given histologic diagnosis.[100–102] This is thought to arise from a multitude of factors including location of care, patient education, poor clinical trial participation, and a lack of a care system focused on the needs of this patient group.[103–107] In addition to osteosarcoma and Ewing sarcoma, sarcomas with a peak incidence in the AYA population include synovial sarcoma and Malignant Peripheral Nerve Sheath Tumor (MPNST).

Current therapy

Excepting gastrointestinal stromal tumor, which is treated with targeted agents primarily, adults with metastatic soft tissue sarcomas have a poor overall survival of roughly 20%–25% at 2 years and a short median survival of 12–18 months, correlated with the grade of tumor and burden of disease. The overall survival has improved over time on patients enrolled prospectively in the early 2000s compared with historical controls in a French database.[108] Patients presenting with poor performance status have significantly shorter survival, with an increased risk of early death within the first 90 days.[109]

The primary therapy for the treatment of localized soft tissue sarcoma is surgery with radiation being used for difficult margins or high grade tumors. Adjuvant chemotherapy is utilized by certain sarcoma centers, but is considered controversial primarily due to potential long-term toxicities and impact upon survival. Intermediate or high-grade soft tissue sarcomas may be treated with neoadjuvant chemotherapy to determine chemosensitivity, induce cytoreduction, and presumably eradicate micrometastasis. Reports on response rates vary across studies due to variations in regimens, dosing schedules, and histologic subtype selection.[110]

Resectable metastatic disease does confer a more favorable prognosis than unresectable, based largely on retrospective, single institution reviews.[111–113] In a series of 97 patients at Massachusetts General Hospital, an increased number of pulmonary lesions, shorter time to progression, bilateral disease, and larger size of disease had inferior survival.[111] Patients with multiple operations lived longer than patients who had undergone only one operation, perhaps secondary to being better candidates for surgery for the aforementioned reasons.[111] Similar factors were found in another review and overall survival was near 50% in both series.[111,113]

Combination therapy for metastatic or unresectable disease, mainly with ifosfamide, has shown benefit in response rate. However, there have been increased toxicities and no clear corresponding benefit in overall survival.[114–118] Response rates to frontline chemotherapy vary considerably in published reports both with single agents and with combinations of chemotherapy with ranges of 10%–46%.[117–127] Confounding this even further are a spectrum of response rates between histologies, whereby synovial cell sarcoma and liposarcoma are more chemosensitive, while leiomyosarcoma and epithelioid sarcoma are less chemosensitive.[124,128] Age also confounds analyses as there are better responses in younger patients.[129–133]

Beyond first-line therapy, gemcitabine and docetaxel are commonly used based on a Sarcoma Alliance for Research through Collaboration (SARC) trial which demonstrated improved activity of the combination of these agents over gemcitabine alone.[124] Response rates were modest by size criteria at 16% overall, and the median progression-free survival (PFS) was just over 6 months. A recently completed trial of the tyrosine kinase inhibitor, pazopanib, demonstrated an improvement in PFS to 4.6 months versus 1.6 months in the placebo arm.[134] This study included previously treated soft tissue sarcomas and excluded liposarcoma patients. Based on these study results, pazopanib was approved by the US Food and Drug Association (FDA) for the treatment of soft tissue sarcoma.

Synovial sarcoma

Based on SEER data and a large, single institution retrospective review, synovial sarcoma accounts for 6%–10% of new sarcoma diagnoses, with 70% of these diagnoses occurring in patients under 40 years old with a peak incidence in the third decade of life.[135] In 2005–2009, synovial sarcoma affected 602 people in the United States, accounting for 5% of STS during that period[136]. Although lung metastases are present in about 6% of newly diagnosed patients, synovial sarcoma can metastasize through the lymph nodes with clinically detectable disease in 15%–20% of newly diagnosed patients.[137,138] Synovial sarcomas are associated with a high risk of recurrence, estimated to be 12% locally and 39% at distant sites at 5 years,[139] with a median survival of 22 months from onset of metastatic disease.[140] Synovial sarcoma is characterized by the presence of a translocation between *SYT* on the X chromosome and *SSX1*, *SSX2*, or *SSX4* on chromosome 18.[141] Fusion type has been explored in terms of prognosis, but size of the primary tumor and presence of metastases at diagnosis are the most significant prognostic variables for synovial sarcoma.[142,143]

Current therapy

Current therapy for synovial sarcoma is similar to that for most adult type STS in the first-line setting, with surgery and radiation for all resectable localized tumors, and chemotherapy being given for larger tumors or metastatic disease. Synovial sarcoma demonstrates better response rates to conventional chemotherapy than other STS, with approximately half of patients responding.[138] Among the STS, synovial sarcoma is particularly sensitive to high doses of ifosfamide, which can be given alone in the second-line setting.[144]

Emerging therapies

Multiple strategies for treating synovial sarcoma have demonstrated some promise. Pazopanib, a multi-tyrosine

kinase inhibitor with antiangiogenic activity, has recently been approved by the FDA for sarcomas and has demonstrated increased progression-free interval, compared with placebo.[134,145] Immunotherapy with T cells targeting NY-ESO, a tumor antigen, has also demonstrated promise in an ongoing trial (NCT01343043).[146] Data from Phase I trials suggest promise for the use of proapoptotic modes of therapy and angiogenesis inhibitors in synovial sarcoma.[147,148]

MPNST

In 2005–2009, MPNST affected 220 people per year in the USA, accounting for 1.8% of all STS.[136] Distant metastasis has been shown in 35 (42%) of 84 patients with pathologically confirmed MPNST from 1999 to 2011.[149] MPNST presents in the context of neurofibromatosis type 1 (NF1) in about half of patients and occurs spontaneously in the other half. NF1 typically is identified either by family history or characteristic skin findings such as café au lait macules, axillary freckling, and/or multiple cutaneous neurofibromas. NF1 affects 1 in 3500 people and is characterized by a mutation in *NF1*, a tumor suppressor gene whose protein product, neurofibromin, is an RAS-GTPase activating protein, which negatively regulates RAS.[150–153] MPNST occurs with a 10% incidence in patients with NF1 and derives from a known precursor lesion, the deep neurofibroma.[154]

Current therapy

Therapy for MPNST is similar to that of most adult type STS in the first-line setting, although it tends to be one of the more chemoresistant histologies and has a poorer prognosis than other histologies.[155,156] An active clinical trial is incorporating etoposide into frontline therapy to establish the response rate and natural history of this malignancy (NCT00304083). Because NF1 patients often have more than one mass and because there are no reliable characteristics that distinguish benign neurofibroma from MPNST by computerized tomography or magnetic resonance imaging, positron emission tomography is particularly useful in distinguishing benign from malignant disease.[157]

Emerging therapies

MPNST associated with NF1 may represent a targetable malignancy with known RAS pathway activation. Although additional molecular changes are also necessary for oncogenesis, an interesting anecdote supporting the homogeneity MPNST development is a case of monozygous twins with remarkably similar phenotypes.[158] Constitutive activation of the RAS/RAF/MEK/ERK pathway through biallelic loss of function of neurofibromin is a uniform and critical event in MPNST pathogenesis.[159,160] mTOR inhibitors have been studied alone in clinical trials for plexiform neurofibromas and in combination for MPNST (NCT01412892). No targeted agent has thus far demonstrated activity to replace the standard of care, although a combination of the mTOR inhibitor everolimus and the anti-angiogenic agent bevacizumab are being explored (NCT01661283). Based on the current knowledge of neurofibromatosis and MPNST, it could be predicted that inhibiting pathways downstream of RAS such as MEK/ERK and PI3K/AKT/mTOR may be promising therapeutic strategies.[161–166]

Leiomyosarcoma

Leiomyosarcomas are sarcomas of smooth muscle origin that generally occur in older patients and account for 10% of all soft tissue sarcomas and 30% of all uterine sarcomas.[167] They can arise in the retroperitoneum, uterus, extremities, blood vessels, and dermis. Unlike sarcomas associated with unbalanced translocation events or activating mutations in a tyrosine kinase receptor, these tumors exhibit complex cytogenetics. Mutations in the *TP53* gene, inactivation of the *PTEN* gene, and mTOR activation have been observed in a subset of tumors.[168]

Current therapy

For patients with extra-uterine leiomyosarcomas, unresectable, metastatic disease is often treated with doxorubicin or doxorubicin-based combinations. Gemcitabine and docetaxel are often considered either in the first or second line setting in leiomyosarcomas with particular activity in uterine leiomyosarcoma.[124,169] Gemcitabine and docetaxel demonstrated a response rate of 53% and PFS was 5.6 months in a single institution series of 35 patients.[121]

Emerging therapies

Unlike other sarcomas with a definable target, leiomyosarcomas appear to be a disease involving a series of aberrations that collectively contribute to its pathogenesis. Loss of cell cycle regulation is inferred by the frequency of p53 inactivation and alterations in RB1 function. Cellular proliferation is commonly impaired in leiomyosarcomas as evidenced by the inactivation of PTEN and upregulation of AKT and mTOR.[170,171] Agents that target the AKT/mTOR pathway are of clear interest for this disease; unfortunately, no large-scale study specific to leiomyosarcomas has been performed.[168] A phase I/IIa trial with ridaforolimus demonstrated a clinical benefit rate, defined by response or stable

disease for at least 4 months in a quarter of the patients.[172] Another Phase II trial demonstrated a medium PFS of 15.3 weeks and a clinical benefit rate of 28.8% for all sarcomas, with this rate being 33% for leiomyosarcomas, the highest subset.[173]

Despite the interest in targeted molecular therapeutics in leiomyosarcomas, a very promising agent is trabectedin, a marine-derived compound that inhibits transcription by forming covalent bonds with the minor groove of DNA. Activity leading to its approval in Europe has been demonstrated in liposarcoma and leiomyosarcoma.[174] Trabectedin also has activity in uterine leiomyosarcoma, as shown in a retrospective series demonstrating a 3-month PFS of 53% and an impressive 6-month PFS of 33%, with mostly stable disease rather than objective responses seen.[175] A Phase II study of 20 patients demonstrated similar findings.[176] Another agent which is being actively explored in a Phase III study is the halichondrin B analog, eribulin, which inhibits microtubules in a novel manner. This agent demonstrated a reasonable progression free rate of 31.6% at 12 weeks in leiomyosarcomas and is being actively studied in comparison to dacarbazine in an ongoing Phase III trial (NCT01327885).[177]

Liposarcoma

Liposarcomas are soft tissue neoplasms of adipocytic lineage, which comprise the single largest group of sarcomas. They affect adults in the overwhelming majority of cases, and are most commonly identified in individuals in their 5th decade of life.[178] The most common site involves the retroperitoneum, but they can also occur in the extremities. The most common form of it is the adipocytic neoplasm, a well-differentiated liposarcoma followed by dedifferentiated liposarcoma, myxoid/round cell liposarcoma, and pleomorphic liposarcoma, which is least common. Well-differentiated liposarcoma and dedifferentiated liposarcoma are considered to be a disease spectrum with low histologic features favoring the well-differentiated disease while the areas of dedifferentiation may closely resemble a high-grade, spindle cell-shaped sarcoma. While both ends of this spectrum are associated with a low-risk (10%) distant metastasis, these diseases can be devastating to local structures, especially in the abdomen. Myxoid liposarcoma, which is characterized by a t(12;16) chromosome translocation between the *CHOP* and *FUS* genes, is a less common entity that typically arises in the extremities and has a predilection for distant metastasis to areas such as the chest wall, paraspinal musculature, retroperitoneum, and the lungs.[179,180]

Current therapy

Liposarcomas are treated by surgical resection. Unfortunately, these tumors are often quite large at diagnosis and provide a significant challenge to the surgical team. Neoadjuvant therapies may be utilized for large, high-grade disease. Chemosensitivity is variable, with well-differentiated and dedifferentiated liposarcomas generally considered insensitive to chemotherapy;[178,181] however, myxoid and pleomorphic liposarcomas may benefit from neoadjuvant chemotherapy. For patients with unresectable/metastatic disease, the primary therapeutic option is chemotherapy. Front-line therapy consists of doxorubicin or doxorubicin compounds, and second-line therapies generally consist of gemcitabine/docetaxel.

Emerging therapies

Each liposarcoma subtype exhibits unique molecular features. Liposarcomas treated as a group by a novel microtubule inhibitor, eribulin, demonstrated nearly stable disease at 3 months in roughly half of patients.[177] Well-differentiated and dedifferentiated liposarcomas frequently exhibit abnormalities in chromosome 12, and approximately 95% of dedifferentiated liposarcomas display up-regulation of HDM2 and CDK4. Recent early-phase studies involving inhibitors of HDM2 and CDK4 have yielded modest results in terms of response and survivorship, although these Phase I studies, which aim to determine an adequate dose, are not powered for response analysis.

As with leiomyosarcomas, trabectedin has shown promising activity, with stable disease shown in a majority of liposarcoma patients and response rates approaching 50% by RECIST (Response Criteria in Solid Tumors).[182–184] Retrospective analyses of responders have shown that trabectedin induces fat maturation similar to that seen with doxorubicin-based regimens and radiation. Liposarcomas were not included in the pazopanib study. Data from a single-institution phase II with sunitinib did show promising 3-month PFS rates for liposarcomas of 75%, suggesting activity.[185]

Conclusion

There is considerable diversity in pathophysiology, current and emerging therapies, and outcome for pediatric and young adult patients with metastatic sarcoma. Some subtypes, such as alveolar rhabdomyosarcoma, Ewing sarcoma, and synovial sarcoma, are well defined in regard to translocations in a majority of cases; however, events that lead to osteosarcoma and embryonal rhabdomyosarcoma are less well understood. Many patients with MPNST have a uniform first hit of a neurofibromin mutation.

Overall, the burden of disease correlates with prognosis in general. When local control is not possible, patients often have a poor prognosis. Patients who can have all areas of disease addressed by surgery or radiation to visible disease often have the best outcomes. Because of years of collaborative studies on these rare tumors, there is a well-established tumor-specific systemic therapy regimen for each histologic type. These tumors are excellent candidates for novel approaches with additional agents as they affect a portion of the population that is motivated toward curative therapy and have demonstrated that they are chemosensitive. Combinations of chemotherapy are the most effective in most settings, and many promising new agents are under active investigation or are being explored in preclinical models. There is a plethora of opportunities to explore these therapies. Ideally, clinical trials will explore multiple promising agents, be studied in a context where historical outcome is known, and will be used for a specific clinical context for a single histology.

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