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SARCOMAS (SR PATEL, SECTION EDITOR)

Advances in Therapy for Pediatric Sarcomas

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Abstract Pediatric sarcomas are relatively rare malignancies individually. As a group they are typically approached with combination chemotherapies in addition to local control. Fortunately, these malignancies have been approached through careful clinical trial collaboration to define risk groups and appropriately deliver local control measures and systemic therapies. Although local disease is typically approached with curative intent, therapy typically lasts over 6 months and has significant associated morbidities. It is more difficult to cure metastatic disease or induce sustained remissions. In this article, we discuss recent advances in the understanding of the disease process and highlight recent and future cooperative group trials in osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, nonrhabdomyosarcoma soft tissue sarcomas, and desmoid tumor as well as discuss promising therapeutic approaches such as epigenetics and immunotherapy.

Keywords Sarcomas · Pediatric sarcomas · Rare malignancies · Oncology · Therapy

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Introduction

Sarcomas are mesenchymal malignancies that affect people of all ages but are relatively more abundant in children than adults. Because of their overall rarity, sarcomas have been classically categorized by histology, primary location (bone versus soft tissue), or cytogenetics (translocation-specific versus complex karyotype). Furthermore, clinical and biological trials to advance our understanding of these sarcomas often require multiple institutions or large cooperative groups. This review discusses the current therapeutic approaches, highlights recent biologic insights, and discusses ongoing or planned clinical trials for the commoner pediatric sarcomas: osteosarcoma, Ewing sarcoma (ES), rhabdomyosarcoma (RMS), nonrhabdomyosarcoma soft tissue sarcomas (NRST S), and desmoid tumor. Additionally, we review emerging data with promising approaches to sarcomas, including epigenetic targeting and immunotherapy.

Osteosarcoma

Osteosarcoma is the commonest primary bone tumor in children and young adults, with an incidence of 4.8 per million per year, peaking in the adolescent age range [1, 2]. The combination of systemic therapy using standard agents such as methotrexate, cisplatin, and doxorubicin along with surgical resection of all clinically detectable metastatic sites is considered the standard therapy for osteosarcoma [3–5]. An important prognostic factor is the extent of disease at presentation, with the lungs being the commonest site of metastases in up to 25 % of newly diagnosed osteosarcoma patients [6]. The ability to achieve complete surgical control of disease is required for cure, and the extent of tumor necrosis after neoadjuvant chemotherapy is another significant prognostic factor [7]. For patients with localized disease, the 10-year overall survival rate is approximately 65 % [8, 9]. Survival rates continue to be unsatisfactory for patients with metastatic and recurrent disease, with 10-year overall survival rates of 25 % [6] and less than 20 % [5], respectively. Over the past two decades, a plateau in the survival and cure rates of osteosarcoma has been reached [10].

Osteosarcoma demonstrates high genetic instability, tumor heterogeneity, local aggressiveness, and early metastatic potential largely because of loss of tumor suppressors rather than targetable oncogenes [11, 12]. Whole-genome sequencing of DNA from osteosarcoma tumor samples and matched normal tissue in a discovery cohort showed single-nucleotide variations exhibited a pattern of localized hypermutation called kataegis in 50 % of these tumors and identified p53 pathway lesions in all the tumors in the discovery cohort [12]. In addition, the *RB1*, *ATRX*, and *DLG2* genes showed recurrent somatic alterations in 29–53 % of the tumors [12]. To date, there are no predictive or prognostic molecular markers for therapy [13]. Ongoing biology efforts through pediatric consortium studies are under way, and tumor specimens from this bank have been used as part of the National Cancer Institute's Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative and the National Cancer Institute-led genome-wide association study [14]. Preclinical drug evaluation systems created for more rapid identification and validation of compounds active in osteosarcoma have been established, such as the Pediatric Preclinical Testing Program in the USA and Innovative Therapies for Children with Cancer in Europe [15].

International collaborations between Europe and the USA are being cultivated to overcome the inherent problem of studying rare cancers. A large international trial for localized osteosarcoma that evaluated intensification of treatment using ifosfamide and etoposide for patients with poor histologic response (less than 90 % necrosis), and addition of interferon in patients with good histologic response (more than 90 % necrosis) has been completed [16]. The addition of interferon did not make a difference in the outcome of patients with good histologic response [17]. A phase 2 trial using trastuzumab (NCT00023998) in addition to standard chemotherapy in patients whose tumors express human epidermal growth factor receptor 2 demonstrated this combination to be tolerable, without demonstrated survival advantage [18]. For patients with newly diagnosed metastatic osteosarcoma, a phase 3 trial which assessed outcome with the addition of liposomal muramyl tripeptide phosphatidylethanolamine to standard chemotherapy (INT-0133) yielded controversial results [9, 19, 20]. A phase 2 study (NCT00742924) in newly diagnosed metastatic osteosarcoma evaluating the addition of zoledronate to standard chemotherapy showed an acceptable toxicity profile [21]. A phase 2 study using aerosolized granulocyte–macrophage colony stimulating factor in patients with a first isolated lung recurrence of osteosarcoma did not show a detectable immunostimulatory effect in osteosarcoma pulmonary metastases, and outcome after relapse was not improved by this agent [22]. Seven completed phase 2 studies through the Children's Oncology Group (COG) and its predecessor groups in children with recurrent/refractory solid tumors did not show activity in osteosarcoma [23–28].

The current direction in osteosarcoma trial development is to identify active agents by either progression-free survival prolongation or response rate in the relapse setting through single-arm phase 2 studies in patients with recurrent osteosarcoma [29]. For patients with recurrent disease, five agents are currently being explored nationally: inhaled liposomal cisplatin, eribulin, glembatumumab, denosumab, and an anti-GD2 antibody. Inhaled liposomal cisplatin has pharmacokinetic properties that maximize lung tissue delivery of cisplatin with minimal systemic exposure and has completed phase 1 testing, with a phase 2 study for patients with lung-only disease in second or third complete radiographic remission ongoing [30]. Eribulin is a fully synthetic analogue of halichondrin B, which is capable of inducing irreversible mitotic blockade and apoptosis by inhibiting microtubule dynamic instability [31]. Complete responses were observed in osteosarcoma xenografts [32]. Denosumab is an antibody targeting receptor activator of nuclear factor κB ligand, which interacts with receptor activator of nuclear factor κB to regulate bone turnover and is expressed by osteosarcoma cells [33, 34]. Antibodies to disialoganglioside GD2, a sialic acid containing glycosphingolipid expressed in over 90 % of osteosarcoma cells, plays an important role in the attachment of tumor cells to extracellular matrix proteins [35, 36]. Glycoprotein nonmetastatic b has recently been identified as a gene that is overexpressed in numerous cancers, often correlates with the metastatic phenotype, and the expression of which in the tumor epithelium is associated with a reduction in disease-free and overall survival. On the basis of these findings, glembatumumab vedotin (CDX-011), an antibody–drug conjugate that selectively targets glycoprotein nonmetastatic b, is another agent of interest in osteosarcoma [37].

Ewing Sarcoma

ES is an aggressive, small round blue cell tumor typically presenting as a primary bone tumor in children and young adults. It has an incidence of three cases per million per year [38]. The diagnosis and understanding of the pathophysiology changed with the identification of a recurrent translocation, typically between the *EWSR1* gene and an ETS family gene (most commonly *FLI1*), in nearly all ES tumors. Current standard therapy for patients with localized ES was derived from two cooperative group trials demonstrating that the addition of treatment with ifosfamide and etoposide to treatment with vincristine/doxorubicin/cyclophosphamide and interval compression (delivering chemotherapy every 2 weeks rather than every 3 weeks) both increased 5-year event-free survival (EFS) in localized, nonpelvic disease [39, 40]. Local control via surgery, radiation therapy, or both remains critically important in disease management. The presence of metastasis at diagnosis is the worst prognostic factor for patients with ES. Roughly 20–30 % of patients present with metastatic disease, and these patients have drastically poorer outcomes [41, 42]. Unfortunately, systemic chemotherapy trials have not been able to improve durable remission rates for patients with metastatic ES.

Direct targeting of the EWS–FLI1 transcription factor has proven difficult; however, there is therapeutic promise in disrupting interactions between EWS–FLI1 and other protein complexes thought to be required for oncogenesis such as RNA helicase and lysine-specific demethylase 1 [43–45]. Mithramycin, an older antibiotic, was identified in a high-throughput drug screen to inhibit ES cell lines as well as ES tumor growth in mouse xenografts [46]. Poly(ADP-ribose) polymerase (PARP) inhibitors are also promising, and have been studied in a variety of malignancies [47–49]. Great interest in this strategy emerged with a small-molecule screen showing a particular sensitivity of EWS–FLI1-postive cells to PARP inhibition [50, 51]. In addition, PARP messenger RNA and proteins are amassed in very high levels in ES cell lines [51]. Although a single-agent study did not show clinical activity, combination studies with temozolomide are being pursued (NCT01858168, NCT02044120). Clinical trials over the past 5 years have focused on insulin-like growth factor receptor 1 (IGF-1R), which is a receptor tyrosine kinase that is overexpressed in ES cells. In early-phase studies, dramatic responses in refractory ES were seen with monoclonal antibodies to IGF-1R, although this was true for only a small subset of patients and with only transient responses [52–56]. Anti-IGF-1R antibodies have been used with mammalian target of rapamycin (mTOR) inhibitors in refractory pediatric patients (as IGF-1R inhibition may block the potential upregulation of Akt seen with mTOR monotherapy [57]), with a few complete responses and sustained stable disease [58, 59]. Anti-IGF-1R antibodies will be used in metastatic patients in a COG study with correlatives planned to attempt to elucidate the mechanisms of tumor cell sensitivity and resistance.

Rhabdomyosarcoma

RMS is the commonest soft tissue sarcoma in childhood, with an annual incidence of 4.4 cases per million, with approximately 350 new cases diagnosed in individuals younger than 20 years each year [60, 61]. Although embryonal RMS accounts for 67 % of the cases in children younger than 10 years, alveolar RMS is commoner in older age groups [60, 61]. More than 70 % of alveolar RMS tumors exhibit characteristic translocations involving the fusion of either the *PAX3* gene (chromosome 2) or the *PAX7* gene (chromosome 1) with the *FOXO1* gene (chromosome 13) [62]. RMS is classified into clinical groups on the basis of the postsurgical extent of disease, regional lymph node involvement, and the presence of distant metastases (Fig. 1). Age at diagnosis, tumor location, lymph node involvement, histologic subtype, and presence of distant metastases are well established prognostic factors [63, 64]. On the basis of clinical group, stage, and histologic subtype, patients are stratified into three risk groups (Fig. 1); low risk (5-year EFS rate greater than 90 %), intermediate risk (5-year EFS rate approximately 65 %), and high risk (5-year EFS rate approximately 20 %). The standard treatment of RMS consists of local control with surgery and/or radiation therapy in conjunction with multiagent chemotherapy, vincristine, actinomycin D and cyclophosphamide (VAC).

Recently completed trials sponsored by the COG have tested therapy reduction for low-risk patients and addition of new agents for high-risk patients. The most recent COG trial for low-risk patients (NCT00075582) reduced the duration of therapy (22 weeks) and the cumulative dose of cyclophosphamide (4.8 g/m^2). Although patients in subset 1 (stages 1–2, groups I–II, group III orbit tumors) had excellent outcome, patients in subset 2 (stage 3, groups I–II and stage 1, group III nonorbit tumors) had inferior outcome compared with historical controls. A phase 2 window trial with vincristine and irinotecan (VI) in high-risk patients showed impressive response rates of 70 % [65], forming the basis of a COG intermediate-risk trial (NCT00354835) comparing VAC treatment and VAC treatment alternating with VI treatment. Although the VAC/VI arm had a lower cumulative cyclophosphamide dose, preliminary results show similar outcomes [66]. Since the VAC/VI arm has potentially less long-term toxicity, this is likely to be the control arm for future intermediate-risk studies [66]. The addition of interval-compressed therapy with VDC/ifosfamide and etoposide and VI to VAC therapy resulted in modest improvement in outcomes for metastatic embryonal RMS, with no improvement in fusion-positive metastatic alveolar RMS [67].

In an effort to identify novel mutations and potential therapeutic targets, whole-genome, whole-exome, and whole transcriptome sequencing were performed in 147 tumor–normal tissue pairs [68]. The overall burden of somatic mutations was low especially in tumors with *PAX3/PAX7* gene fusion. In 45 %

Risk Group	Histology	Stage	Clinical Group
Low (Subset 1)	ERMS	1	I, II
		1	III (Orbit)
		2	I, II
Low (Subset 2)		1	III (Non-orbit)
		3	I, II
Intermediate	ERMS	2, 3	III
	ARMS	1, 2, 3	I, II, III
High	ERMS, ARMS	4	IV

STAGE

Stage	Site	Size	Regional Nodes	Metastasis
1	Favorable*	Any	Any	No
2	Unfavorable†	≤ 5 cm	No/unknown	No
3	Unfavorable	≤ 5 cm	Yes	No
	Unfavorable	> 5 cm	Any	No
4	All	Any	Any	Yes

* Orbit, Head and Neck (excluding parameningeal), Genitourinary (non-bladder/prostate), Biliary tract/ Liver

† Cranial/Parameningeal, Bladder/Prostate, Other (e.g. trunk, retroperitoneum)

CLINICAL GROUP

I	Localized disease, completely resected	
II	Evidence of regional spread	Grossly resected with microscopic residual disease
		Regional disease with involved nodes, Completely resected with no microscopic residual disease
		Regional disease with involved nodes, Grossly resected with microscopic residual disease or histologic involvement of more distal regional node
III	Gross residual disease	After biopsy only
		Gross or major resection of primary (> 50%)
IV	Distant metastatic disease	

Fig. 1 Risk group stratification for rhabdomyosarcoma. *ARMS* alveolar rhabdomyosarcoma, *ERMS* embryonal rhabdomyosarcoma

of fusion-negative tumors, the RAS pathway (including *FGFR4*, RAS, *NF1*, and *PIK3CA*) was mutationally activated. This opens up the possibility for testing agents that target this pathway such as trametinib in RMS. In another study, targeted sequencing of 29 genes in 89 RMS tumor samples was performed; mutations were found in only 20 % of the samples. *FGFR4* mutations were present in 9.3 % of embryonal tumors [69]. Ponatinib, a potent *FGFR4* inhibitor, has demonstrated efficacy in preclinical models of RMS [70]. However, given the rarity of the disease and the small subpopulation involved, novel trial designs are needed to carry forward such agents into clinical practice.

Preclinical studies have identified several potential new agents that may be useful in the treatment of patients with RMS. The inhibition of vascular endothelial growth factor (VEGF) and mTOR has shown promising results in preclinical models of RMS [71–73]. A randomized phase 2 design has been adopted to identify active agents in relapsed patients with the aim of moving the identified agents to upfront therapy. The first of these trials compared VEGF inhibition (bevacizumab) with mTOR inhibition (temsirolimus) in the context of background therapy with cyclophosphamide and vinorelbine (NCT01222715). The study was terminated early owing to a lower number of failures in the temsirolimus arm which met the predetermined stopping rule (Leo Mascarenhas, personal communication). Future intermediate-risk and high-risk studies will likely test the addition of temsirolimus to the existing therapy. Inhibition of IGF-1R has demonstrated promise in preclinical models of RMS [74]. To investigate this further, the COG has conducted a pilot study (NCT01055314), which terminated in 2013, incorporating an anti-IGF-1R monoclonal antibody which will be compared with the addition of the alkylating agent temozolomide for patients with newly diagnosed high-risk RMS. These results are highly anticipated.

Nonrhabdomyosarcoma Soft Tissue Sarcomas

NRSTS account for 4 % of all childhood malignancies, affecting at least 500 individuals under the age of 20 years in the USA each year [1]. Standard therapy for these tumors has traditionally involved a combination of surgery with or without chemotherapy and radiation therapy. Prognostic risk factors include size, grade, stage, and margin status. These factors were prospectively studied for the first time through a recently completed COG study (NCT00346164) and were used to direct treatment allocation (Table 1). Low-risk patients, which account for about 60 % of the population, have excellent long-term survival [75, 76]. However, high doses of radiation therapy are required for certain subsets of these patients, which may lead to significant long-term complications [77, 78]. The survival rates for patients with intermediate-risk and high-risk disease, which account for about 40 % of the population, are approximately 50 % and 15 %, respectively [75, 76]. The chemotherapy backbone of ifosfamide and doxorubicin is considered to be the most active and among the most

Table 1 Nonrhabdomyosarcoma soft tissue sarcoma staging and treatment proposal

Risk group	Factors				Proposed treatment
	Grade	Size	Stage	Initial resectability	
Low	Low	Any	Nonmetastatic	Gross resection	Observation
	High	<5 cm	Nonmetastatic	Without microscopic margins	Observation
	High	<5 cm	Nonmetastatic	With microscopic margins	Adjuvant radiation therapy
Intermediate	High	>5 cm	Nonmetastatic	Gross resection	Adjuvant chemotherapy and radiation therapy
	High	>5 cm	Nonmetastatic	Unresected	Neoadjuvant chemoradiotherapy, surgery, adjuvant chemotherapy with or without radiation therapy
High	Low	Any	Metastatic	Gross resection	Observation
	High	Any	Metastatic	Gross resection	Adjuvant chemotherapy and radiation therapy
	High	Any	Metastatic	Unresected	Neoadjuvant chemoradiotherapy, surgery, adjuvant chemotherapy with or without radiation therapy

commonly used regimens in NRSTS [79]. Although this chemotherapy combination is considered the "standard of care," the radiographic response rate and outcomes remain poor for those with large, high-grade tumors and those with unresectable or metastatic disease [80, 81].

Unlike other solid tumor treatment models using a "one-size-fits-all" strategy, NRSTS is made up of a variety of distinct histologic subtypes, suggesting that a more individualized approach to therapy may be required. An expanding subset of subtypes has identified translocations [e.g., dermatofibrosarcoma protuberans: t(17;22)(q21;q13)] and actionable mutations (e.g., gastrointestinal stromal tumor: Kit, *PDGFRA*) that may be able to be treated with "targeted" agents, though this is still largely in a discovery phase [82–85]. Considerable progress on elucidating the pathogenesis of translocated transcription factors has been made by investigating protein complex interactions in synovial sarcoma [86]. When taken as a whole, NRSTS demonstrate extreme biological heterogeneity across each of the histologic subtypes, with suspected involvement of multiple signaling pathways in tumorigenesis [87–89].

To facilitate trial accrual and advancements in NRSTS, the COG is currently taking the approach of grouping all histologic subtypes together but evaluating novel multitargeted agents that could impact the majority of histologic subtypes. Pazopanib, a multitargeted tyrosine kinase inhibitor, is a potent inhibitor of VEGF receptor, platelet-derived growth factor receptor, and c-Kit, which are some of the most prevalent and dysregulated proteins across NRSTS histologic subtypes [90–93]. Pazopanib has demonstrated activity in adults with advanced soft tissue sarcomas and is currently FDA-approved for recurrent, previously treated soft tissue sarcomas [94–96]. A COG phase 1 study of pazopanib in children with relapsed or refractory solid tumors was recently conducted (NCT00929903) and established the maximal tolerated dose and manageable side effects [97]. A phase 2 single-agent study in children with refractory solid tumors, including NRSTS, is currently under development. Since single-drug approaches have not traditionally had a great impact on outcome, combining a multitargeted agent with traditional cytotoxic chemotherapy may maximize the benefit as demonstrated with other disease types [98, 99]. Building on the above-mentioned principles, an upcoming collaborative cooperative group study between the COG and NRG Oncology will investigate adding pazopanib in combination with radiation therapy or chemoradiotherapy in pediatric and adult patients newly diagnosed with intermediate-risk and high-risk NRSTS. The backbone therapy will be influenced by patient and tumor characteristics as well as the "chemotherapy sensitivity" of a particular histologic subtype. Since standard imaging may not be the ideal measure of response for these tumor types especially when evaluating targeted therapies, novel efficacy end points (e.g., pathologic and positron emission tomography response rates) will be compared with historical measures [82, 100]. This joint study represents a unique and unprecedented opportunity to advance the treatment of both pediatric and adult NRSTS. The correlative studies will collect the largest sample of pediatric and adult NRSTS to understand the similarities and differences between them and potentially identify other actionable targets for future development. Finding that some mutations are independent of NRSTS histologic subtype will support the notion that functional classification of NRSTS based on molecular defects may more accurately guide the use of personalized anticancer therapy in this patient population.

Desmoid Tumor

Desmoid tumors arise from fibroblasts that demonstrate a propensity for locally invasive growth and local disease

recurrence, but without the ability to metastasize. The overall incidence of desmoid tumor is estimated to be two to four new cases per million people per year [101, 102]. There are clinical associations (e.g., familial adenomatous polyposis syndrome, Gardner's syndrome, tuberous sclerosis) that along with β-catenin mutations have helped to gain insight into desmoid tumor disease biology and pathogenesis [103–105].

Historically, the standard therapy for desmoid tumor in children has involved surgery in symptomatic, extremity cases. The completeness of initial surgical resection is the most important factor influencing EFS, although even in this situation recurrences can be common [106–108]. Radiation therapy is another treatment option, but outcomes have been mixed and largely depend on the disease burden at the time of treatment [107, 109, 110]. However, this modality is rarely used in children since long-term morbidity in this vulnerable population can be significant [110].

A number of cytotoxic and noncytotoxic agents have been used in children with differing degrees of success [107, 111–115]. Unfortunately, almost all the reported studies are retrospective and involve small numbers, making it difficult to reach any definitive conclusions. The most widely used systemic chemotherapy regimen for unresectable or recurrent desmoid tumor in children is vinblastine and methotrexate. However, one of the largest, prospective pediatric desmoid tumor trials to date demonstrated a 2-year progression-free survival rate of 46 % and a median time to disease progression of 15.9 months after therapy was stopped [116]. Further, up to two thirds of subjects experienced grade 3 or grade 4 toxicity. In a more targeted therapy approach, a recently completed pediatric prospective study incorporated high-dose tamoxifen and sulindac on the basis of evidence of increased estrogen receptor expression within desmoid tumors. This regimen demonstrated limited activity (2-year progression-free survival rate of 36 %), although toxicities were minimal aside from a relatively high incidence of asymptomatic ovarian cyst formation [117]. More recently, a conservative "wait and see" approach has been proposed for a certain subset of patients who may not require upfront therapy [118, 119]. Ideally, a future prospective trial in children would incorporate a natural history arm to properly answer this question.

Given the less-than-ideal outcomes of previous therapeutic approaches, there is a need to evaluate other drugs that may be more effective, be better tolerated, and take advantage of known or theoretical pathways in desmoid tumorigenesis. As an example, a current multi-institutional pilot study is evaluating the role of the mTOR pathway in desmoid tumor (NCT01265030). Other potential therapeutic targets include the Wnt signaling pathway due to known *APC* and β-catenin mutations in some patients with desmoid tumor [120, 121]. Currently there are no national trials under development or open for children with desmoid tumor. The few adult open clinical trials do not allow for enrollment of children (NCT01981551, NCT02066181). Despite the rarity of this tumor, the accrual success of the last two prospective trials run through the COG reflects the eagerness of patients and providers to enroll in appealing trials for this patient population. Moreover, much needed tumor specimen banking is strongly associated with trial enrollment.

Immunotherapy

Immunotherapy using antibodies, immune adjuvants, vaccination, and adoptive cellular therapy has been used in pediatric sarcoma. As our knowledge of the immune system expands, it is likely there will be new opportunities for using this novel approach in combination therapy. It is plausible that by combining the antibodies with the appropriate combination therapy in certain sarcomas, biochemotherapy might be of benefit [29].

Tumor vaccine strategies may have a role in sarcoma, but will likely require delivery in combination with other strategies [122]. These could include a dendritic cell vaccine (NCT01803152) and novel vaccines such as secreted heat shock protein [123]. Despite interest in cytokine therapy, inhaled granulocyte–macrophage colony stimulating factor has not altered the landscape of therapy for osteosarcoma [22]. New strategies targeting immune tolerance, such as the cytotoxic T-lymphocyte antigen 4 blocking antibody ipilimumab, which is approved for treatment of melanoma, are of interest for sarcoma [124]. ES that is metastatic at presentation was associated with increased levels of regulatory T cells, which impair the immune response to tumor [125]. Ipilimumab decreases the levels of regulatory T cells by blocking the signaling of B7 through cytotoxic T-lymphocyte antigen 4 and favoring the signaling of B7 through cluster of differentiation 28 [126]. Programmed cell death 1 and its ligand are also involved in immune tolerance to tumors and can be blocked by antibodies [127]. Given the recent approval of ipilimumab, blockade of tumor tolerance through immune checkpoint modulation is of great interest in sarcoma. Ipilimumab has been tested in a limited number of adult synovial sarcoma patients without clear evidence of benefit, but in a study that was limited in enrollment [128]. It is being further evaluated at the National Cancer Institute in children with a variety of cancers, including sarcoma (NCT01445379).

Adoptive transfer of lymphocytes has been explored for treatment of sarcoma. High-dose therapy is given before infusion of cells, which can deplete inhibitory cells, allowing the transferred cells to proliferate and activate. Allogeneic natural killer cells may target cancer in the minimal disease setting (NCT01287104). Some studies have used T cells with an engineered T-cell receptor that recognizes NY-ESO-1, demonstrating tumor regression in a patient with synovial sarcoma

[129, 130]. In an attempt to generate a graft-versus-tumor effect, allogeneic hematopoietic stem cell transplant has been attempted in sarcoma patients, but has not been successful clinically to date [131]

Epigenetics

Epigenetics is the study of heritable changes in gene expression produced by noncoding changes to DNA and has emerged as an attractive target for translocation-defined tumors. Most clinical attempts at influencing epigenetic changes include the use of histone deacetylase inhibitors. Histone deacetylase inhibitors could play a role in combination therapy with both immunotherapy and classic chemotherapy. Entinostat is a novel histone deacetylase inhibitor specific for class I and class III histone deacetylases, and has been associated with a clinical response in a patient with ES [132], as well as potentially improving the antigenicity of tumor cells in ES and susceptibility to chemotherapy [133, 134]. The Pediatric Preclinical Testing Program has also demonstrated activity in vitro of vorinostat in pediatric osteosarcoma models [135]. Although histone deacetylase inhibitors are unlikely to be of benefit in pediatric sarcoma as single agents, the newer agents may play a role in combination therapy either in salvage or as part of upfront therapy, a strategy endorsed by the leadership in national group settings. Additionally, epigenetic modifiers are being combined with immunotherapy to upregulate antigens, and there are active clinical trials exploring the interaction between demethylating agents and tumor vaccines (e.g., NCT01241162) [136].

Conclusions

Pediatric sarcoma care has benefitted from a rich history of collaborative clinical trials that have established a standard of care in these rare tumors (Table 2). In general, a non-metastatic presentation which is amenable to local control, typically surgery, with systemic chemotherapy results in a sustained complete remission rate of 70 % at 5 years. Metastatic presentation portends a worse prognosis and correlates with the extent and burden of metastases. There are comprehensive strategies for identification and testing of agents in the

Table 2 Pediatric sarcoma disease treatment summary (USA)

Disease	Standard of care	Current and recently closed pediatric trials
Osteosarcoma	Surgery, chemotherapy (MAP)	A Randomized Trial of the European and American Osteosarcoma Study Group to Optimize Treatment Strategies for Resectable Osteosarcoma Based on Histological Response to Pre-operative Chemotherapy (NCT00134030)
		Feasibility and Dose Discovery Analysis of Zoledronic Acid with Concurrent Chemotherapy in the Treatment of Newly Diagnosed Metastatic Osteosarcoma (NCT00742924)
Ewing sarcoma	Surgery, chemotherapy (VDC, IE), radiation therapy	A Phase III Randomized Trial of Adding Vincristine-Topotecan-Cyclophosphamide to Standard Chemotherapy in Initial Treatment of Non-metastatic Ewing Sarcoma (NCT01231906)
Rhabdomyosarcoma	Surgery, chemotherapy (VAC), radiation therapy	Randomized Study of Vincristine, Dactinomycin and Cyclophosphamide (VAC) versus VAC Alternating with Vincristine and Irinotecan (VI) for Patients with Intermediate-Risk Rhabdomyosarcoma (RMS) (NCT00354835)
		A Pilot Study to Evaluate Novel Agents (Temozolomide and Cixutumumab [IMC-A12, Anti-IGF-IR Monoclonal Antibody, IND #100947, NSC #742460]) in Combination with Intensive Multi-agent Interval Compressed Therapy for Patients with High-Risk Rhabdomyosarcoma (NCT01055314)
		A Randomized Phase II Trial of Bevacizumab (IND# 7921, Avastin) and Temsirolimus (IND# 61010, Torisel) in Combination with Intravenous Vinorelbine and Cyclophosphamide in Patients with Recurrent/Refractory Rhabdomyosarcoma (NCT01222715)
Nonrhabdomyosarcoma soft tissue sarcoma	Surgery, chemotherapy (ID), radiation therapy	Risk-Based Treatment for Non-Rhabdomyosarcoma Soft Tissue Sarcomas in Patients Under 30 Years of Age (NCT00346164)
Desmoid tumor	Surgery, chemotherapy (VbM)	A Pilot Study Evaluating the Use of the mTOR Inhibitor Sirolimus in Children and Young with Desmoid-Type Fibromatosis (NCT01265030)

ID ifosfamide, doxorubicin; *IE* ifosfamide, *MAP* high-dose methotrexate, cisplatin, doxorubicin; cyclophosphamide; etoposide; *VAC* vincristine, actinomycin D, cyclophosphamide; *VbM* vinblastine, methotrexate; *VDC* vincristine, doxorubicin

commoner subtypes of pediatric sarcoma along with large efforts such as TARGET and the Pediatric Cancer Genome Project that are systematically mining the genomic landscapes for insight into tumorigenesis and novel treatment strategies. Promising newer manifestations of immunotherapies are just beginning to be explored, with corresponding biologic advances. Furthermore, epigenetic approaches may hold promise for translocation-defined sarcomas and may allow targeting of protein complexes associated with translocated transcription factors, previously considered undruggable. Finally, collaboration amongst large pediatric and adult oncology consortia will facilitate a more consolidated clinical trials network which may allow greater accrual for these rare subtypes and rapid translation of biologic discoveries.

Compliance with Ethics Guidelines

Conflict of Interest Aaron Weiss, Jonathan Gill, John Goldberg, Joanne Lagmay, Holly Spraker-Perlman, Rajkumar Venkatramani, and Damon Reed declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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