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SARCOMAS (SR PATEL, SECTION EDITOR)

Advances in the Management of Pediatric Sarcomas

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Abstract

Purpose of Review The prognosis of pediatric patients who present with metastatic or recurrent sarcomas remains poor. In this review, we summarize the advances in the management of metastatic and relapsed pediatric sarcoma by highlighting recent and future clinical trials.

Recent Findings Research into the identification of novel therapies for refractory pediatric sarcomas continues to advance. Outcomes have not improved in several decades underlying a need for improved understanding of the biology behind these tumors and the identification of novel therapeutic molecular targets that can be exploited pharmacologically. Multiple challenges remain for novel therapy in sarcomas such as the selection of effective targets, management of toxicities, and the tumor microenvironment.

Summary Many unique challenges remain in the treatment of patients with refractory pediatric sarcomas. Multiple strategies and targets are under investigation that hold promise.

Keywords Sarcomas · Pediatric sarcomas · Immunotherapy · Therapy

Introduction

Sarcomas are tumors of mesenchymal origin believed to arise from bone or soft tissue precursors. While broadly rare—accounting for only about 1% of all cancers in the general population—they represent approximately 13% of cancers in patients who are under the age of 20 [1]. Pediatric sarcomas are largely divided between those that arise from bone, and those that arise from soft tissue. The most common malignant tumors of bone are osteosarcoma and Ewing sarcoma (ES), while rhabdomyosarcoma (RMS) is the most common sarcoma of soft tissue. Other non-RMS soft tissue sarcomas such as desmoplastic small round cell and synovial sarcoma, become more common as children age into adolescence and young adulthood [2]. Current treatment regimens rely on a combination of systemic chemotherapy, surgery, and radiation therapy and have resulted in 5-year event-free survival (EFS) rates of 60–70% depending on the specific histologic diagnosis and presence of metastatic disease. Patients with metastatic disease have a poor prognosis with 5-year EFS rates in the 20–30% range. Patients with disease recurrence fare even poorer with EFS less than 20% [3, 4].

In this review, we summarize recent advances in the management of pediatric sarcomas with a brief overview of current therapeutic options followed by a review of active and recently closed clinical trials that have explored novel biologic targets and immunotherapy.

Osteosarcoma

Osteosarcoma is the most common malignant tumor of bone, with an incidence of 4.8 per million per year. Unfortunately, there have been no significant therapeutic breakthroughs in several decades despite extensive clinical investigation [1, 5, 6]. The current standard of care for patients with osteosarcoma comprises surgical resection of all detectable disease in conjunction with systemic chemotherapy using a backbone of methotrexate, doxorubicin, and cisplatin [7–9]. For patients

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with localized disease, this treatment regimen yields a 5-year EFS of approximately 65% for patients with localized disease [10, 11]. The overall survival (OS) rates for patients who present with metastatic or recurrent disease remain poor, approaching approximately 25% and less than 20%, respectively [12], and as such, the presence of distant metastasis remains a key prognostic indicator [13]. The most common site of metastasis in osteosarcoma is the lungs, which is seen in up to 25% of newly diagnosed patients [14].

Recent clinical trials have failed to show improvement in progression-free survival (PFS) or response rates in the relapsed disease setting. Osteosarcoma is genomically complex with high heterogeneity characterized by chromosomal instability, including deletions, duplications, and other somatic variants [15]. Tumors with high genomic complexity such as osteosarcoma potentially have several neoantigens that may be exploited for novel molecular therapy. The Children's Oncology Group (COG) has recently evaluated several targeted agents that had shown promise in preclinical studies of osteosarcoma. Glembatumumab vedotin (CDX-011) (NCT02487979) is a well-tolerated antibody-drug conjugate that selectively targets glycoprotein non-metastatic b (or osteoactivin), which is expressed on the surface of osteosarcoma cells [16, 17]. The agent exhibited moderate antitumor activity in a phase 2 clinical trial but did not meet the bar to move forward to full clinical evaluation [18]. Eribulin mesylate induces an irreversible mitotic blockade and apoptosis by inhibiting microtubule dynamic instability. Eribulin mesylate had shown activity in osteosarcoma xenografts, and although it was well tolerated in a clinical study, it did not evoke sufficient response either to warrant further evaluation in a phase III trial [19]. Nuclear factor–κB is a transcription factor known to regulate bone turnover recently found to be expressed by osteosarcoma cells [20]. Denosumab is a human monoclonal antibody that targets the receptor activator of nuclear factor–κB ligand (RANKL) with activity in patients diagnosed with giant cell tumor of bone where the protein is also expressed [21]. Based on these data, the agent was recently evaluated in a phase II study (AOST 1321) in patients with recurrent osteosarcoma by the COG [22, 23]. At this time, data from this clinical trial is pending.

There is growing clinical evidence that multi-targeted tyrosine kinase inhibitors have efficacy in osteosarcoma. The SARC0024 trial evaluated regorafenib, a multi-kinase inhibitor, in 42 adult patients with metastatic osteosarcoma and showed that the median PFS duration was 3.6 months, double that seen in the placebo group [24•]. A case series of 15 patients treated with pazopanib showed one partial response (7%) and a median PFS duration of 6 months [25]. A phase II trial of cabozantinib in patients with osteosarcoma and Ewing sarcoma reported a 6-month PFS rate of 33%, a median PFS duration of 6.2 months, and a partial response in five of 42 patients (12%) in the osteosarcoma cohort (NCT02243605) [26].

Immune checkpoint inhibitors have been studied in osteosarcoma, and while initial preclinical data were promising, the results in vivo have been disappointing. Both CTLA-4 and PD-1 are targets that have shown significant control of tumor spread in sarcoma mouse models [27–31]. One study showed elevated expression of CTLA-4 in T cells collected from 20 pediatric sarcoma patients (11 osteosarcoma and nine ES), as compared to those from healthy controls suggesting a role for immune checkpoint blockade, particularly in osteosarcoma [32]. A recent phase I study (NCT01445379) treated pediatric patients with recurrent or refractory solid tumors with CTLA-4 blockade via ipilimumab. This study, which included 8 patients with osteosarcoma, demonstrated increased activation of cytotoxic T lymphocytes without increased infiltration of regulatory T cells. Unfortunately, no objective tumor regression was observed [33]. While the results with immune checkpoint inhibitors have been disappointing, genetically modified cell therapy may yet hold promise. Specifically, CAR T cells have been evaluated in osteosarcoma. A phase I clinical trial evaluating anti-Her-2 CAR T cells in patients with advanced pediatric sarcoma—the majority of whom had osteosarcoma—demonstrated a median OS duration of 10.3 months (NCT00902044) [34]. A current clinical trial using CAR T cells that target the GD2 glycoprotein, which is expressed in osteosarcoma, is ongoing (Table 1).

Ewing Sarcoma

ES is a sarcoma of bone or soft tissue composed of small round blue cells thought to be of either the neural crest or mesenchymal lineage [35–37]. The majority of cases of ES are thought to arise from an oncoprotein produced by rearrangement between EWSR1 on chromosome 22 and FLI1 on chromosome 11 [38]. ES is the second most common type of primary bone cancer in the USA, with an annual incidence in patients younger than 20 years of 2.9 per million [1]. It accounts for approximately 25% to 34% of malignant bone tumors [1, 6], making it the second most common bone tumor of childhood and adolescence after osteosarcoma. Similar to osteosarcoma, patients with metastatic or recurrent disease have a dismal prognosis compared to patients with localized ES. The 5-year OS rate for patients with localized ES is ranges from 65 to 75% with current therapy. Patients who present with metastatic disease have a 5-year OS rate of less than 30%, although patients with isolated pulmonary metastasis fare slightly better (approximately 50%) [39, 40]. Patients with recurrence have a 5-year OS rate of approximately 10% [38]. The standard of care for ES is alternating cycles of interval-compressed vincristine, doxorubicin, cyclophosphamide, and ifosfamide and etoposide (VDC/IE) [40–42]. Currently, there remains no established standard backbone therapy for patients with recurrent or refractory ES, and

Table 1 Current clinical trials for pediatric patients with refractory or recurrent sarcomas

Clinical trial	Disease	Therapeutic intervention	Target/action	Phase
NCT02502786	Recurrent osteosarcoma	Humanized anti-GD2 antibody (Hu3F8) and GM-CSF*	GD2	II
NCT01953900	Refractory or metastatic GD2 positive sarcoma	Anti-GD2 chimeric antigen receptor T cells in VZV	GD2	I
NCT02484443	Recurrent osteosarcoma	Dinutuximab + GM-CSF	GD2	II
NCT03600649	Relapsed or refractory Ewing sarcoma	SP2577-seclidemstat	LSD-1	I
NCT02657005	Relapsed or refractory Ewing sarcoma	TK216	RNA Helicase A	I
NCT02173093	Osteosarcoma	GD2-bi-specific activated T cells	GD2	I/II
NCT00902044	Sarcomas	Anti-Her2 CAR T-cells	HER2	I
NCT02409576	Metastatic EWS, metastatic osteosarcoma,	Haploidentical NK cell infusions	NK cell therapy	I
NCT03006848	Recurrent or progressive osteosarcoma	Avelumab	Anti PD-L1	II
NCT01738139	Advanced solid tumors	Ipilimumab + imatinib	Anti-CTL4 + TKI	I
NCT02901145	Recurrent solid tumors	Nivolumab + cyclophosphamide	Anti PD-L1	I
NCT02793466	Relapsed or refractory solid tumors	Durvalumab	IgG1k monoclonal antibody	I
NCT02100891	RMS, EWS, neuroblastoma, osteosarcomas	AHCT** + NK cell infusion	Bone marrow transplantation + NK cell therapy	II
NCT02867592	Recurrent or refractory RMS, EWS, osteosarcoma	Cabozantinib	c-MET, vascular endothelial growth factor receptor, and TKs	II
NCT03210714	Advanced solid tumors	Erdafitinib	FGFR	II
NCT03441360	Relapsed or refractory RMS, non-RMS soft tissue sarcoma, and EWS	Eribulin mesylate	Microtubule-depolymerizing	II
NCT03245450	Refractory or recurrent solid tumors, non-RMS soft tissue sarcoma, and EWS	Eribulin mesylate + irinotecan hydrochloride	Microtubule-depolymerizing	II
NCT03041701	Rhabdomyosarcoma	Ganitumab	Insulin-like growth factor 1 receptor	II
NCT03213704	Recurrent or Refractory solid tumors	Larotrectinib	NTRK	II
NCT00840047	RMS, EWS, osteosarcoma, and neuroblastoma	Methionine	Protein formation	II
NCT02945800	RMS, osteosarcoma, EWS, and soft tissue sarcoma	Nab-paclitaxel + gemcitabine	Microtubule-depolymerizing + DNA synthesis	II
NCT03233204	Recurrent or refractory solid tumors	Olaparib	PARP	II
NCT03526250	Recurrent or refractory solid tumors	Palbociclib	CDK4/6	II
NCT02048371	RMS, liposarcoma, osteogenic sarcoma, and Ewing/Ewing-like sarcoma	Regorafenib	Multi-receptor tyrosine kinases	II
NCT03213678	Recurrent or Refractory Solid tumors	Samotolisib	PI3K/mTOR	II
NCT02574728	RMS, brain tumors, neuroblastoma, osteosarcoma, EWS, Wilms tumors, and soft tissue sarcomas	Sirolimus + celecoxib + etoposide + cyclophosphamide	IL-2, COX-2, topoisomerase II, alkylating	II
NCT03213665	Recurrent or refractory solid tumors	Tazemetostat	EZH2, SMARCB1, SMARCA4	II
NCT03220035	Recurrent or refractory solid tumors	Vemurafenib	BRAF V600	II
NCT02567435	Rhabdomyosarcoma	VAC/VI** vs. VAC/VI plus temsirolimus	Standard therapy + mTOR inhibitor	III
NCT01343043	Synovial sarcoma	Genetically engineered NY-ESO-1	NY-ESO-1 and TCR	I

*Granulocyte-macrophage colony-stimulating factor

**Allogeneic hematopoietic cell transplantation (AHCT)

**Vincristine, dactinomycin, and cyclophosphamide alternating with vincristine and irinotecan (VAC/VI)

similar to other refractory pediatric sarcoma histologies—there remains a vital need for novel therapies.

A phase III trial (COG AEWS1221) comparing the combination of insulin-like growth factor 1 receptor antibody ganitumab and VDC/IE with VDC/IE alone [43] in patients with metastatic or refractory ES was recently performed by the COG, and data is pending at this time [43]. Several clinical trials have attempted to exploit the EWS-FLI1 translocation as a potential therapeutic target. EWS-FLI1 is known to drive the expression of proteins that regulate microtubule stability. As in osteosarcoma, eribulin mesylate has been studied for the treatment of ES. A COG phase I trial showed a partial response for 4 cycles in a patient with ES [44]. Currently, there are two trials evaluating eribulin for relapsed ES (Table 1). Recent preclinical data has suggested that targeting the epigenetics of EWS/FlI1 may hold promise. Lysine-specific-demethylase 1 (LSD-1) has shown high expression in ES. In preclinical models, the enzyme is essential in driving the transcriptional repression of the EWS/FLI1 oncoprotein through direct binding of the oncoprotein via the NuRD-LSD1 complex [45]. LSD-1 inhibitors preclinically have been shown to impede tumorigenesis in ES models [46]. A phase I clinical trial is currently underway exploring the LSD-1 inhibitor, seclidemstat, for patients with refractory ES (Table 1). Another small molecule inhibitor of EWS/Fli1 oncogenesis is similarly undergoing clinical evaluation in ES—YK-4-279/TK216—having been shown in vitro to inhibit the binding of RNA helicase A with the EWS/FLI1 oncoprotein leading to decreased growth in orthotopic xenografts [47]. This phase I clinical trial is currently recruiting patients.

As in osteosarcoma, multi-target kinase inhibitors have also been extensively evaluated for ES. ES patients have demonstrated partial responses to pazopanib, which is FDA approved for adult soft tissue sarcoma, in several case reports; however, there was evidence of resistance after prolonged use [48, 49]. Cabozantinib, another multi-targeted TKI, was evaluated in a phase II trial for recurrent ES; the results showed tumor control, with nine (27.7%) partial responses and 10 (30.3%) stable disease [26, 50••].

Rhabdomyosarcoma

RMS is the most common soft tissue sarcoma in the pediatric population, with an annual incidence of 4.5 cases per 1 million [51, 52]. The majority of cases are diagnosed in the first decade of life, and there is a slight association with familial cancer syndromes such as Li-Fraumeni syndrome, neurofibromatosis, and Beckwith-Wiedmann syndrome [52]. The genitourinary tract and head and neck region are the most commonly affected sites; patients with lesions in the extremities have an inferior prognosis as compared to other primary sites [53]. Histologically, RMS may be categorized into embryonal, alveolar, pleomorphic, and sclerosing subtypes [52, 54]. Embryonal RMS is the most common subtype seen in pediatrics and historically has been associated with a superior prognosis as compared to the second most common subtype—alveolar RMS [52]. RMS is divided into two distinct genotypes on the basis of the presence or absence of PAX-FOXO1 gene rearrangement: fusion-positive RMS and fusion-negative RMS [52]. Recent data suggests that the inferior prognosis of patients with alveolar RMS is likely related to the majority of alveolar cases harboring the PAX-FOXO1 translocation [52, 55, 56, 57••]. The OS rate of RMS varies widely depending on the child's age and the tumor's location, stage, and risk group. Children aged 1 to 9 years old have a better prognosis than do children who are older or younger [58]. The 5-year OS rate for children who have low-risk RMS ranges from 70 to 90%. The 5-year OS rate for children in the intermediate-risk group ranges from 50 to 70%, while children who have high-risk RMS have a 5-year OS rate of 20–30% [58]. Patients with relapsed disease have a poorer outcome, with a 5-year OS rate ranging from 5 to < 20% [59]. Historically, frontline patients are treated with vincristine, actinomycin D, and cyclophosphamide, which has been the standard of care for RMS, along with surgery or radiation therapy, for the last five decades [52].

Because of the poor survival outcomes of patients with high-risk and recurrent RMS, molecular-targeted therapy and immunotherapy approaches have been emerging; these methods are associated with a decrease in treatment-associated toxicity compared with standard chemotherapy [55]. Patients with fusion-positive RMS could benefit from PAX-FOXO1–targeted therapy that acts directly to its upstream transcription factor and can control subsequent signaling cascades and other target genes. However, preclinical and clinical studies have failed to demonstrate better outcomes with PAX-FOXO1–targeted therapy compared with standard therapy [55].

Clinical trials using targeted therapies against single point mutations that act within the receptor tyrosine kinase/RAS/PIK3A pathways have failed to improve outcomes; these pathways require further study to become a future point of intervention [55]. Table 1 summarizes the current clinical trials that are recruiting patients (phases I, II, and III).

Synovial Sarcoma

Synovial sarcoma (SS) is a rare and aggressive high-grade malignancy representing 8–10% of all soft tissue sarcoma cases, which makes it the most common non-RMS soft tissue sarcoma in children and adolescents [60, 61]. SS can arise at any age but predominantly affects individuals aged 15–35 years, with one-third of all patients being younger than 20 years at diagnosis [62]. SS is a mesenchymal neoplasm

with variable epithelial differentiation and a specific reciprocal *t*(*x*:18)(p11.2;q11.2) chromosomal translocation comprised of fusion of the SS18 gene and one of three closely related genes (SSX1, SSX2, or SSX4). Histologically, both pediatric and adult SS can be subdivided into monophasic, biphasic, and poorly differentiated subtypes [63]. Pediatric patients with SS have an improved prognosis compared to adults; however, both have a poor prognosis when they present with metastatic disease (5–11% of pediatric cases) [60, 64].

Over the last three decades, a rise in the incidence of SS has been seen, with no change in the survival rate [65]. Therapy for pediatric SS is determined by the size of the tumor at diagnosis and the ability to achieve a full surgical resection, the presence of metastatic disease, and the histologic grade of the tumor. Certain pediatric patients whose tumors are small and can be fully resected will be cured with surgery alone [66]. Pediatric SS patients with high-risk features such as a large primary tumor or the presence of metastatic disease at diagnosis will often be treated with systemic chemotherapy that includes doxorubicin and ifosfamide, radiotherapy for local control, and surgery [61]. Options for patients who suffer recurrent or progressive disease are limited. Unfortunately, clinical trials of immune checkpoint inhibitors, such as pembrolizumab, nivolumab, and ipilimumab, have not shown promise for SS; however, other immunotherapies may provide benefit [61]. NY-ESO-1 is a highly immunogenic cancer-testes antigen that is expressed in 70–80% of SS [67]. It has been targeted using both vaccines and adoptive cell therapy [68, 69]. In a phase I study, 11 of 18 adults with metastatic disease experienced a partial response using genetically engineered T cells that were reactive with NY-ESO-1 [70]. Another study using genetically engineered T cells showed similar response rates in conjunction with the long-term persistence of NY-ESO-1 T cells [71]. Currently, a pilot study in children is being conducted that further evaluates adoptive immunotherapy with T cells that have been engineered to recognize the NY-ESO-1 peptide [61] (Table 1).

Desmoplastic Small Round Cell Tumor

Desmoplastic small round cell tumor (DSRCT) is an extremely aggressive, rare soft tissue sarcoma that frequently presents with diffuse abdominal sarcomatosis in mostly male adolescents and young adults [72, 73, 74•, 75]. Patients present with non-specific symptoms of abdominal pain or distention, nausea, constipation, and weight loss that do not improve with medical management [72, 73, 74•]. Notwithstanding the profound molecular profiling of DSRCT, its findings have not resulted in useful salvage therapeutic strategies, and the 5-year OS rate remains lower than 15% [76].

Morphologically, DSRCTs are characterized by polyphenotypic differentiation, as evidenced by immunohistochemical staining for epithelial, mesenchymal, and neural markers, including cytokeratins, desmin and vimentin, and neuron-specific enolase, respectively [77]. These tumors are distinguished by a pathognomonic chromosomal translocation that pairs the ES gene (EWSR1) with the Wilm's tumor suppressor gene (WT1) (EWSR1-WT1 *t*(11;22)(p13:q12)) [73].

The treatment for DSRCT comprises neoadjuvant and adjuvant chemotherapy using regimens that are typically reserved for ES [73]. Combinations such as VDC/IE (vincristine, doxorubicin, cyclophosphamide/ifosfamide, and etoposide), VIT (vincristine, irinotecan, and temozolomide), and VAI (vincristine, doxorubicin, and ifosfamide) have resulted in favorable yet short-lived responses [72, 73, 75]. High-dose chemotherapy, followed by autologous hematopoietic stem cell rescue, has not been associated with improved outcomes [73]. Complete surgical cytoreduction followed by consolidative whole-abdomen radiotherapy at a dose of 30 Gy, with or without a focal boost, are frequently used in an attempt to reduce the frequency of intra-abdominal recurrence [72, 73, 74•, 75, 78]. The role of hyperthermic intraperitoneal chemotherapy is still under clinical investigation [73]. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy with heated cisplatin (given at a dose of 100 to 150 mg/m^2) may provide benefit to a limited number of patients; however, it does not seem to improve survival in DSRCT patients with hepatic or portal metastasis [74•]. Novel therapies such as [90Y]Yttrium microsphere radioembolotherapy could have a role in patients with hepatic disease [79].

Multi-targeted receptor tyrosine kinase inhibitors of vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and c-KIT, such as pazopanib, sunitinib, and apatinib, have shown positive responses in selected cases [72, 80, 81]. Lurbinectedin, a synthetic DNA binder that leads to the formation of DNA double-strand breaks, was recently revealed to have preliminary activity in DSRCT (NCT02448537) [82].

Immunotherapy for DSRCT is being explored. Advanced immune landscape profiling is being used to identify innovative therapeutic strategies for these sarcomas (NCT03967834). A phase I/II trial is evaluating the checkpoint kinase 1 inhibitor prexasertib in combination with irinotecan and temozolomide after prexasertib was found to have a robust antitumor effect with complete regression in two DSRCT patient-derived xenografts (NCT04095221). Targeting the immunomodulatory molecule B7H3 through the monoclonal antibody 8H9 is another targeted therapy under evaluation. A phase II trial of intraperitoneal radioimmunotherapy with 131I-8H9 is presently taking place (NCT04022213). DSRCT is a rare orphan tumor with limited therapeutic opportunities. Longitudinal profiling could help us discover prospective targets that could improve patient survival.

Challenges in Immunotherapy

Immunotherapy remains an attractive therapeutic option to evaluate in pediatric sarcomas, especially adoptive cell therapy such as CAR T cells. Unfortunately, the degree of benefit seen with this treatment modality in hematologic malignancies has not yet been translated to pediatric sarcomas likely related to multiple inherent challenges of using this therapy in solid tumors. The identification of suitable target antigens that ensure the effective elimination of tumor cells while avoiding the off-tumor or on-target toxicity that is caused by T cells attacking healthy tissues remains a significant challenge in solid tumors. In addition, target antigens expressed in sarcomas tend to be heterogeneous, differing not only from each other but also from the primary and metastatic stages of the same tumor.

One strategy to avoid the off-tumor and on-target toxicity that is observed with CAR T cell therapy for sarcomas is to use tumor-associated antigens that elicit immune responses that are strictly tumor-specific such as viral antigens, antigens that result from a mutation or a rearrangement of a gene-coding sequence, or antigens that are specifically encoded by cancer-germline genes [83]. An example of tumor-associated antigens are neoantigens, which are short amino acid peptides that are created by cancer cell genome mutations and have been identified in ovarian and gastrointestinal cancers, as well as in melanoma [84, 85]. There is preclinical and clinical evidence that confirms neoantigens as potential targets for adoptive T cell therapy in solid tumors [86–88]. Recently, a first-in-humans trial showed that tumor-associated antigen cytotoxic T cells that targeted WT1, PRAME, and survivin safely induced disease stabilization, prolonged time to disease progression, and decreased levels of circulating tumor antigen DNA [89]. A separate challenge facing immunotherapy strategies in sarcomas is the tumor microenvironment, which is complex in pediatric sarcomas and contributes to tumorigenesis and metastasis in and of itself by limiting immune responses to cancer cells and preventing the eradication of tumors potentiated by tumor-associated macrophages, fibroblasts, and myeloid-derived suppressor cells. Immunomodulatory strategies to counteract the tumor microenvironment are urgently needed, as are approaches to improve T cell trafficking and persistence. Other immunotherapy strategies to consider in pediatric sarcomas include utilizing highly tumor-specific T cell treatments that can be generated for any patient with T cells that recognize tumor mutations. This can be achieved by using genetically modified polyclonal T cells to express T cell receptors that recognize neoantigens in the context of the major histocompatibility complex [85]. Adoptive cell therapy with gamma delta cells are another tentative option in which the TCR recognizes unprocessed antigens independent of the MHC complex.

Conclusions

Pediatric sarcomas are in many cases curable with frontline standard of care therapy, however, several challenges remain, and the outcomes for patients who present with metastatic disease or suffer disease recurrence remain poor. Identifying novel treatments—such as targeted therapies as well as immunotherapies—will be needed to improve outcomes for patients with high-risk or recurrent pediatric sarcomas and is an area of active research.

Compliance with Ethical Standards

Conflict of Interest Fiorela N. Hernandez Tejada, Alejandro Zamudio, Mario L. Marques-Piubelli, and Branko Cuglievan declare no conflict of interest. Douglas Harrison receives 2% salary support from Salarius Pharmaceuticals, which supports one of the clinical trials for Ewing sarcoma cited in this article (phase I trial of LSD-1 inhibitor, seclidemstadt).

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

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Ries LAG SM, Gurney JG, Linet M, Tamra T, Young JL, Bunin GR (eds). Cancer incidence and survival among children and adolescents: United States SEER Program 1975-1995. National Cancer Institute, SEER program; Bethesda, MD, 1999.
2. Williams RF, Fernandez-Pineda I, Gosain A. Pediatric Sarcomas. Surg Clin North Am. 2016;96(5):1107–25.
3. Anderson JL, Denny CT, Tap WD, Federman N. Pediatric sarcomas: translating molecular pathogenesis of disease to novel therapeutic possibilities. Pediatr Res. 2012;72(2):112–21.
4. Hingorani P, Janeway K, Crompton BD, Kadoch C, Mackall CL, Khan J, et al. Current state of pediatric sarcoma biology and opportunities for future discovery: a report from the sarcoma translational research workshop. Cancer Genet. 2016;209(5):182–94.
5. Smith MA, Seibel NL, Altekruse SF, Ries LA, Melbert DL, O'Leary M, et al. Outcomes for children and adolescents with cancer: challenges for the twenty-first century. J Clin Oncol. 2010;28(15):2625–34.
6. al. BAe. Cancer epidemiology in older adolescents and young adults 15 to 29 years of age, including SEER incidence and survival: 1975-2000. National Cancer Institute; Bethesda, MD, 2006.
7. Kempf-Bielack B, Bielack SS, Jurgens H, Branscheid D, Berdel WE, Exner GU, et al. Osteosarcoma relapse after combined modality therapy: an analysis of unselected patients in the cooperative Osteosarcoma Study Group (COSS). J Clin Oncol. 2005;23(3):559–68.
8. Federman N, Bernthal N, Eilber FC, Tap WD. The multidisciplinary management of osteosarcoma. Curr Treat Options in Oncol. 2009;10(1–2):82–93.

9. Bielack SS, Carrle D, Hardes J, Schuck A, Paulussen M. Bone tumors in adolescents and young adults. Curr Treat Options in Oncol. 2008;9(1):67–80.
10. Meyers PA, Schwartz CL, Krailo M, Kleinerman ES, Betcher D, Bernstein ML, et al. Osteosarcoma: a randomized, prospective trial of the addition of ifosfamide and/or muramyl tripeptide to cisplatin, doxorubicin, and high-dose methotrexate. J Clin Oncol. 2005;23(9):2004–11.
11. Ferrari S, Smeland S, Mercuri M, Bertoni F, Longhi A, Ruggieri P, et al. Neoadjuvant chemotherapy with high-dose Ifosfamide, high-dose methotrexate, cisplatin, and doxorubicin for patients with localized osteosarcoma of the extremity: a joint study by the Italian and Scandinavian Sarcoma Groups. J Clin Oncol. 2005;23(34):8845–52.
12. Weiss A, Gill J, Goldberg J, Lagmay J, Spraker-Perlman H, Venkatramani R, et al. Advances in therapy for pediatric sarcomas. Curr Oncol Rep. 2014;16(8):395.
13. Bielack SS, Kempf-Bielack B, Delling G, Exner GU, Flege S, Helmke K, et al. Prognostic factors in high-grade osteosarcoma of the extremities or trunk: an analysis of 1,702 patients treated on neoadjuvant cooperative osteosarcoma study group protocols. J Clin Oncol. 2002;20(3):776–90.
14. Kager L, Zoubek A, Potschger U, Kastner U, Flege S, Kempf-Bielack B, et al. Primary metastatic osteosarcoma: presentation and outcome of patients treated on neoadjuvant Cooperative Osteosarcoma Study Group protocols. J Clin Oncol. 2003;21(10):2011–8.
15. Champiat S, Ferte C, Lebel-Binay S, Eggermont A, Soria JC. Exomics and immunogenics: bridging mutational load and immune checkpoints efficacy. Oncoimmunology. 2014;3(1):e27817.
16. Lettieri CK, Appel N, Labban N, Lussier DM, Blattman JN, Hingorani P. Progress and opportunities for immune therapeutics in osteosarcoma. Immunotherapy. 2016;8(10):1233–44.
17. Roth M, Linkowski M, Tarim J, Piperdi S, Sowers R, Geller D, et al. Ganglioside GD2 as a therapeutic target for antibody-mediated therapy in patients with osteosarcoma. Cancer. 2014;120(4):548–54.
18. Kopp LM, Malempati S, Krailo M, Gao Y, Buxton A, Weigel BJ, et al. Phase II trial of the glycoprotein non-metastatic B-targeted antibody-drug conjugate, glembatumumab vedotin (CDX-011), in recurrent osteosarcoma AOST1521: a report from the Children's Oncology Group. Eur J Cancer. 2019;121:177–83.
19. Isakoff MS, Goldsby R, Villaluna D, Krailo MD, Hingorani P, Collier A, et al. A phase II study of eribulin in recurrent or refractory osteosarcoma: a report from the Children's Oncology Group. Pediatr Blood Cancer. 2019;66(2):e27524.
20. Mori K, Le Goff B, Berreur M, Riet A, Moreau A, Blanchard F, et al. Human osteosarcoma cells express functional receptor activator of nuclear factor-kappa B. J Pathol. 2007;211(5):555–62.
21. Chawla S, Blay JY, Rutkowski P, Le Cesne A, Reichardt P, Gelderblom H, et al. Denosumab in patients with giant-cell tumour of bone: a multicentre, open-label, phase 2 study. Lancet Oncol. 2019;20(12):1719–29.
22. Mori K, Berreur M, Blanchard F, Chevalier C, Guisle-Marsollier I, Masson M, et al. Receptor activator of nuclear factor-kappaB ligand (RANKL) directly modulates the gene expression profile of RANK-positive Saos-2 human osteosarcoma cells. Oncol Rep. 2007;18(6):1365–71.
23. Lamoureux F, Richard P, Wittrant Y, Battaglia S, Pilet P, Trichet V, et al. Therapeutic relevance of osteoprotegerin gene therapy in osteosarcoma: blockade of the vicious cycle between tumor cell proliferation and bone resorption. Cancer Res. 2007;67(15):7308–18.
24.• Davis LE, Bolejack V, Ryan CW, Ganjoo KN, Loggers ET, Chawla S, et al. Randomized Double-Blind Phase II Study of Regorafenib in Patients With Metastatic Osteosarcoma. J Clin Oncol. 2019;37(16):1424–31 **The SARC0024 trial demonstrated activity of regorafenib, a multi-kinase inhibtor in patients with progressive metastatic osteosarcoma.**
25. Longhi A, Paioli A, Palmerini E, Cesari M, Abate ME, Setola E, et al. Pazopanib in relapsed osteosarcoma patients: report on 15 cases. Acta Oncol. 2019;58(1):124–8.
26. Italiano A, Mir O, Mathoulin-Pelissier S, Penel N, Piperno-Neumann S, Bompas E, et al. Cabozantinib in patients with advanced Ewing sarcoma or osteosarcoma (CABONE): a multicentre, single-arm, phase 2 trial. Lancet Oncol. 2020;21(3):446–55.
27. Kim JR, Moon YJ, Kwon KS, Bae JS, Wagle S, Kim KM, et al. Tumor infiltrating PD1-positive lymphocytes and the expression of PD-L1 predict poor prognosis of soft tissue sarcomas. PLoS One. 2013;8(12):e82870.
28. van Dam LS, de Zwart VM, Meyer-Wentrup FAG. The role of programmed cell death-1 (PD-1) and its ligands in pediatric cancer. Pediatr Blood Cancer. 2015;62(2):190–7.
29. Lussier DM, O'Neill L, Nieves LM, McAfee MS, Holechek SA, Collins AW, et al. Enhanced T-cell immunity to osteosarcoma through antibody blockade of PD-1/PD-L1 interactions. J Immunother. 2015;38(3):96–106.
30. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012;366(26):2443–54.
31. Lussier DM, Johnson JL, Hingorani P, Blattman JN. Combination immunotherapy with α-CTLA-4 and α-PD-L1 antibody blockade prevents immune escape and leads to complete control of metastatic osteosarcoma. J Immunother Cancer. 2015;3:21.
32. Hingorani P, Maas ML, Gustafson MP, Dickman P, Adams RH, Watanabe M, et al. Increased CTLA-4(+) T cells and an increased ratio of monocytes with loss of class II (CD14(+) HLA-DR(lo/neg)) found in aggressive pediatric sarcoma patients. J Immunother Cancer. 2015;3:35.
33. Merchant MS, Wright M, Baird K, Wexler LH, Rodriguez-Galindo C, Bernstein D, et al. Phase I clinical trial of Ipilimumab in pediatric patients with advanced solid tumors. Clin Cancer Res. 2016;22(6):1364–70.
34. Ahmed N, Brawley VS, Hegde M, Robertson C, Ghazi A, Gerken C, et al. Human epidermal growth factor receptor 2 (HER2) - specific chimeric antigen receptor-modified T cells for the immunotherapy of HER2-positive sarcoma. J Clin Oncol. 2015;33(15):1688–96.
35. von Levetzow C, Jiang X, Gwye Y, von Levetzow G, Hung L, Cooper A, et al. Modeling initiation of Ewing sarcoma in human neural crest cells. PLoS One. 2011;6(4):e19305.
36. Tirode F, Laud-Duval K, Prieur A, Delorme B, Charbord P, Delattre O. Mesenchymal stem cell features of Ewing tumors. Cancer Cell. 2007;11(5):421–9.
37. Hu-Lieskovan S, Zhang J, Wu L, Shimada H, Schofield DE, Triche TJ. EWS-FLI1 fusion protein up-regulates critical genes in neural crest development and is responsible for the observed phenotype of Ewing's family of tumors. Cancer Res. 2005;65(11):4633–44.
38. Lawlor ER, Sorensen PH. Twenty years on: what do we really know about Ewing sarcoma and what is the path forward? Crit Rev Oncog. 2015;20(3–4):155–71.
39. Gaspar N, Hawkins DS, Dirksen U, Lewis IJ, Ferrari S, Deley M-CL, et al. Ewing sarcoma: current management and future approaches through collaboration. J Clin Oncol. 2015;33(27):3036–46.
40. Womer RB, West DC, Krailo MD, Dickman PS, Pawel BR, Grier HE, et al. Randomized controlled trial of interval-compressed chemotherapy for the treatment of localized Ewing sarcoma: a report from the Children's Oncology Group. J Clin Oncol. 2012;30(33):4148–54.

41. Grier HE, Krailo MD, Tarbell NJ, Link MP, Fryer CJ, Pritchard DJ, et al. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. N Engl J Med. 2003;348(8):694–701.
42. Ladenstein R, Potschger U, Le Deley MC, Whelan J, Paulussen M, Oberlin O, et al. Primary disseminated multifocal Ewing sarcoma: results of the Euro-EWING 99 trial. J Clin Oncol. 2010;28(20):3284–91.
43. NCT02306161: National Cancer Institute RPTEtAotI-RMAGA, NSC# 750008) to multiagent chemotherapy for patients with newly diagnosed metastatic Ewing sarcoma. In: ClinicalTrials.gov (cited 2020, Jan 27).
44. Schafer ES, Rau RE, Berg S, Liu X, Minard CG, D'Adamo D, et al. A phase 1 study of eribulin mesylate (E7389), a novel microtubule-targeting chemotherapeutic agent, in children with refractory or recurrent solid tumors: a Children's Oncology Group Phase 1 Consortium study (ADVL1314). Pediatr Blood Cancer. 2018;65(8):e27066.
45. Theisen ER, Pishas KI, Saund RS, Lessnick SL. Therapeutic opportunities in Ewing sarcoma: EWS-FLI inhibition via LSD1 targeting. Oncotarget. 2016;7(14):17616–30.
46. Sankar S, Theisen ER, Bearss J, Mulvihill T, Hoffman LM, Sorna V, et al. Reversible LSD1 inhibition interferes with global EWS/ETS transcriptional activity and impedes Ewing sarcoma tumor growth. Clin Cancer Res. 2014;20(17):4584–97.
47. Erkizan HV, Kong Y, Merchant M, Schlottmann S, Barber-Rotenberg JS, Yuan L, et al. A small molecule blocking oncogenic protein EWS-FLI1 interaction with RNA helicase A inhibits growth of Ewing's sarcoma. Nat Med. 2009;15(7):750–6.
48. Attia S, Okuno SH, Robinson SI, Webber NP, Indelicato DJ, Jones RL, et al. Clinical activity of pazopanib in metastatic extraosseous Ewing sarcoma. Rare Tumors. 2015;7(2):5992.
49. Alcindor T. Response of refractory Ewing sarcoma to pazopanib. Acta Oncol. 2015;54(7):1063–4.
50.•• Bailey K, Cost C, Davis I, Glade-Bender J, Grohar P, Houghton P, et al. Emerging novel agents for patients with advanced Ewing sarcoma: a report from the Children's Oncology Group (COG) new agents for Ewing sarcoma task force. F1000Res. 2019;8:F1000 Faculty Rev-493. https://doi.org/10.12688/f1000research.18139.1.. **The COGs New Agents for Ewing Sarcoma Task Force present an evaluation of new agents with the higuest priority to treat metastatic and relapse Ewing Sarcoma.**
51. Ognjanovic S, Linabery AM, Charbonneau B, Ross JA. Trends in childhood rhabdomyosarcoma incidence and survival in the United States, 1975-2005. Cancer. 2009;115(18):4218–26.
52. Shern JF, Yohe ME, Khan J. Pediatric Rhabdomyosarcoma. Crit Rev Oncog. 2015;20(3–4):227–43.
53. Casanova M, Meazza C, Favini F, Fiore M, Morosi C, Ferrari A. Rhabdomyosarcoma of the extremities: a focus on tumors arising in the hand and foot. Pediatr Hematol Oncol. 2009;26(5):321–31.
54. Chowdhury T, Barnacle A, Haque S, Sebire N, Gibson S, Anderson J, et al. Ultrasound-guided core needle biopsy for the diagnosis of rhabdomyosarcoma in childhood. Pediatr Blood Cancer. 2009;53(3):356–60.
55. Chen C, Dorado Garcia H, Scheer M, Henssen AG. Current and future treatment strategies for rhabdomyosarcoma. Front Oncol. 2019;9:1458.
56. Stewart E, McEvoy J, Wang H, Chen X, Honnell V, Ocarz M, et al. Identification of therapeutic targets in rhabdomyosarcoma through integrated genomic, epigenomic, and proteomic Analyses. Cancer Cell. 2018;34(3):411–26.e19.
57.•• Hibbitts E, Chi YY, Hawkins DS, Barr FG, Bradley JA, Dasgupta R, et al. Refinement of risk stratification for childhood rhabdomyosarcoma using FOXO1 fusion status in addition to established clinical outcome predictors: a report from the Children's Oncology Group. Cancer Med. 2019;8(14):6437–48 **This report established that in patients with metastatic RMS, FOXO1 status is the most important prognostic factor.**
58. Oberlin O, Rey A, Lyden E, Bisogno G, Stevens MC, Meyer WH, et al. Prognostic factors in metastatic rhabdomyosarcomas: results of a pooled analysis from United States and European cooperative groups. J Clin Oncol. 2008;26(14):2384–9.
59. Malempati S, Hawkins DS. Rhabdomyosarcoma: review of the Children's Oncology Group (COG) Soft-Tissue Sarcoma Committee experience and rationale for current COG studies. Pediatr Blood Cancer. 2012;59(1):5–10.
60. Sultan I, Rodriguez-Galindo C, Saab R, Yasir S, Casanova M, Ferrari A. Comparing children and adults with synovial sarcoma in the Surveillance, Epidemiology, and End Results program, 1983 to 2005: an analysis of 1268 patients. Cancer. 2009;115(15):3537–47.
61. Stacchiotti S, Van Tine BA. Synovial sarcoma: current concepts and future perspectives. J Clin Oncol. 2018;36(2):180–7.
62. Hale R, Sandakly S, Shipley J, Walters Z. Epigenetic targets in synovial sarcoma: a mini-review. Front Oncol. 2019;9:1078.
63. Fletcher CDM, World Health Organization, International Agency for Research on Cancer. WHO classification of tumours of soft tissue and bone. 4th ed. Lyon: IARC Press; 2013. p. 468.
64. Ferrari A, De Salvo GL, Oberlin O, Casanova M, De Paoli A, Rey A, et al. Synovial sarcoma in children and adolescents: a critical reappraisal of staging investigations in relation to the rate of metastatic involvement at diagnosis. Eur J Cancer. 2012;48(9):1370–5.
65. Wang S, Song R, Sun T, Hou B, Hong G, Mallampati S, et al. Survival changes in patients with synovial sarcoma, 1983-2012. J Cancer. 2017;8(10):1759–68.
66. Ferrari A, Chi Y-Y, De Salvo GL, Orbach D, Brennan B, Randall RL, et al. Surgery alone is sufficient therapy for children and adolescents with low-risk synovial sarcoma: a joint analysis from the European paediatric soft tissue sarcoma Study Group and the Children's Oncology Group. Eur J Cancer. 2017;78:1–6.
67. Tesfaye M, Savoldo B. Adoptive cell therapy in treating pediatric solid tumors. Curr Oncol Rep. 2018;20(9):73.
68. Takeoka T, Nagase H, Kurose K, Ohue Y, Yamasaki M, Takiguchi S, et al. NY-ESO-1 protein cancer vaccine with poly-ICLC and OK-432: rapid and strong induction of NY-ESO-1-specific immune responses by poly-ICLC. J Immunother. 2017. https://doi.org/10.1097/CJI.0000000000000162.
69. Robbins PF, Morgan RA, Feldman SA, Yang JC, Sherry RM, Dudley ME, et al. Tumor regression in patients with metastatic synovial cell sarcoma and melanoma using genetically engineered lymphocytes reactive with NY-ESO-1. J Clin Oncol. 2011;29(7):917–24.
70. Robbins PF, Kassim SH, Tran TL, Crystal JS, Morgan RA, Feldman SA, et al. A pilot trial using lymphocytes genetically engineered with an NY-ESO-1-reactive T-cell receptor: long-term follow-up and correlates with response. Clin Cancer Res. 2015;21(5):1019–27.
71. D'Angelo SP, Melchiori L, Merchant MS, Bernstein D, Glod J, Kaplan R, et al. Antitumor activity associated with prolonged persistence of adoptively transferred NY-ESO-1 (c259)T cells in synovial sarcoma. Cancer Discov. 2018;8(8):944–57.
72. Subbiah V, Lamhamedi-Cherradi SE, Cuglievan B, Menegaz BA, Camacho P, Huh W, et al. Multimodality treatment of desmoplastic small round cell tumor: chemotherapy and complete cytoreductive surgery improve patient survival. Clin Cancer Res. 2018;24(19):4865–73.
73. Menegaz BA, Cuglievan B, Benson J, Camacho P, Lamhamedi-Cherradi SE, Leung CH, et al. Clinical activity of pazopanib in patients with advanced desmoplastic small round cell tumor. Oncologist. 2018;23(3):360–6.
74•. . Hayes-Jordan AA, Coakley BA, Green HL, Xiao L, Fournier KF, Herzog CE, et al. Desmoplastic small round cell tumor treated with

cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: results of a phase 2 trial. Ann Surg Oncol. 2018;25(4):872–7 **This Phase 2 clinical trial provides evidence of survival benefit of cytoreductive surgery plus HIPEC in patients with DSRCT.**

75. Hayes-Jordan A, LaQuaglia MP, Modak S. Management of desmoplastic small round cell tumor. Semin Pediatr Surg. 2016;25(5):299–304.
76. Lal DR, Su WT, Wolden SL, Loh KC, Modak S, La Quaglia MP. Results of multimodal treatment for desmoplastic small round cell tumors. J Pediatr Surg. 2005;40(1):251–5.
77. Fine RL, Shah SS, Moulton TA, Yu IR, Fogelman DR, Richardson M, et al. Androgen and c-Kit receptors in desmoplastic small round cell tumors resistant to chemotherapy: novel targets for therapy. Cancer Chemother Pharmacol. 2007;59(4):429–37.
78. Verret B, Honore C, Dumont S, Terrier P, Adam J, Cavalcanti A, et al. Trabectedin in advanced desmoplastic round cell tumors: a retrospective single-center series. Anti-Cancer Drugs. 2017;28(1):116–9.
79. Subbiah V, Murthy R, Anderson PM. [90Y]yttrium microspheres radioembolotherapy in desmoplastic small round cell tumor hepatic metastases. J Clin Oncol. 2011;29(11):e292–e4.
80. Italiano A, Kind M, Cioffi A, Maki RG, Bui B. Clinical activity of sunitinib in patients with advanced desmoplastic round cell tumor: a case series. Target Oncol. 2013;8(3):211–3.
81. Shi C, Feng Y, Zhang LC, Ding DY, Yan MY, Pan L. Effective treatment of apatinib in desmoplastic small round cell tumor: a case report and literature review. BMC Cancer. 2018;18(1):338.
82. Cote GM, Choy E, Chen T, Marino-Enriquez A, Morgan J, Merriam P, et al. A phase II multi-strata study of lurbinectedin as a single agent or in combination with conventional chemotherapy in metastatic and/or unresectable sarcomas. Eur J Cancer. 2020;126:21–32.
83. Kakarla S, Gottschalk S. CAR T cells for solid tumors: armed and ready to go? Cancer J. 2014;20(2):151–5.
84. Gros A, Parkhurst MR, Tran E, Pasetto A, Robbins PF, Ilyas S, et al. Prospective identification of neoantigen-specific lymphocytes in the peripheral blood of melanoma patients. Nat Med. 2016;22(4):433–8.
85. Pasetto A, Gros A, Robbins PF, Deniger DC, Prickett TD, Matus-Nicodemos R, et al. Tumor- and neoantigen-reactive T-cell receptors can be identified based on their frequency in fresh tumor. Cancer Immunol Res. 2016;4(9):734–43.
86. Blankenstein T, Leisegang M, Uckert W, Schreiber H. Targeting cancer-specific mutations by T cell receptor gene therapy. Curr Opin Immunol. 2015;33:112–9.
87. Deniger DC, Pasetto A, Robbins PF, Gartner JJ, Prickett TD, Paria BC, et al. T-cell responses to TP53 "hotspot" mutations and unique neoantigens expressed by human ovarian cancers. Clin Cancer Res. 2018;24(22):5562–73.
88. Parkhurst MR, Robbins PF, Tran E, Prickett TD, Gartner JJ, Jia L, et al. Unique neoantigens arise from somatic mutations in patients with gastrointestinal cancers. Cancer Discov. 2019;9(8):1022–35.
89. Hont AB, Cruz CR, Ulrey R, O'Brien B, Stanojevic M, Datar A, et al. Immunotherapy of relapsed and refractory solid tumors with ex vivo expanded multi-tumor associated antigen specific cytotoxic T lymphocytes: a phase I study. J Clin Oncol. 2019;37(26):2349–59.