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REVIEW ARTICLE

Systemic therapy in pediatric-type soft-tissue sarcoma

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ABSTRACT

Soft-tissue sarcoma (STS) is rare and represents approximately 7% of cancers in children and in adolescents less than 20 years of age. Rhabdomyosarcoma (RMS) is most prevalent in children less than 10 years of age and peaks again during adolescence (16–19 years of age). Multi-agent chemotherapy constitutes the mainstay of treatment for RMS. In other non-rhabdomyosarcoma soft-tissue tumours, such as synovial sarcoma, evidence for routine use of chemotherapy is less robust, and alternative treatment options, including targeted agents and immunotherapy, are being explored. In this review, we focus on chemotherapy for pediatric-type RMS and discuss the advances and challenges in systemic treatment for select non-rhabdomyosarcoma soft-tissue tumours in children and adolescents. We support an increasingly cooperative approach for treating pediatric and adult STS.

Key Words Chemotherapy, pediatrics, adolescents and young adults, AYAs, rhabdomyosarcoma, non-rhabdomyosarcoma, soft-tissue sarcoma

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INTRODUCTION

Soft-tissue sarcoma (STS) of childhood represents a heterogeneous group of malignancies, primarily of mesenchymal cell origin, that can develop anywhere in the body. The age-adjusted rate of STS for children less than 20 years of age has been reported to be 11.0 per million, which constitutes 7% of all primary malignancies for that population[1]. Most of these STSs (40%) are rhabdomyosarcoma (RMS) and include the biologically distinct histologic subtypes embryonal RMS (eRMS) and alveolar RMS (aRMS)[1]. Those entities present with a bimodal age distribution: a larger peak between 0 and 5 years of age in which eRMS predominates, and a smaller peak during adolescence[2].

The formation of large cooperative groups, such as the Intergroup Rhabdomyosarcoma Study Group (IRSG) and the Children's Oncology Group (COG), has improved patient outcomes, largely because of the introduction of risk-adapted protocols and better supportive care. The 5-year survival rate for eRMS has increased to 73.4% in 2000 from 52.7% in 1976[2]. Comparatively, the survival rate for aRMS improved marginally between 1996 and 2000, to 47.8% from 40.1%[2]. The intention of systemic chemotherapy in RMS has been to eliminate micrometastatic disease. Most trials use risk stratification based on pathology and clinical staging systems to determine assigned treatment. Also, RMS is highly sensitive to radiation therapy (RT); local control, although mandatory, can therefore be achieved with RT alone or with surgery plus RT. Multi-agent chemotherapy has remained the mainstay of treatment for RMS, but efforts to improve suboptimal survival rates for aRMS are ongoing.

Non-rhabdomyosarcoma (nrSTS) constitutes 4% of childhood cancers[1] and has a bimodal age distribution, with a propensity for infants and for adolescents and young adults. Distinct pathology and molecular subtypes distinguish these heterogeneous rare mesenchymal tumours, which are less chemosensitive than RMS. Limited and outdated prospective clinical trial data support chemotherapy for nrSTS[3–5]. The role for systemic therapy remains controversial, but it can be incorporated into a risk-assigned strategy based on tumour size, extent of surgical resection, and presence of metastases[6]. In contrast to the approach for RMS, definitive surgical resection of the primary tumour is the mainstay treatment for all nrSTSs. Furthermore, because of the long-term consequences, the role of RT is a topic of interest in younger patients, although RT remains central for adults with STS. Chemotherapy seems preferable for unresectable or metastatic disease, and increasingly, novel therapeutic approaches are being sought as earlier treatment options.

In the present review, we focus on systemic treatment for pediatric STS, with a focus on RMS and how chemotherapy

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has evolved to the current standard of care. We outline biologic advances that are steering trials toward genomic risk stratification and incorporation of targeted agents. We discuss the biology, the current role for chemotherapy, and the new approaches to management for select nrSTS entities: infantile fibrosarcoma, synovial sarcoma, *BCOR* and *CIC*-rearranged sarcomas, and desmoplastic small round-cell tumour (DSRCT).

METHODS

Search Strategy and Selection Criteria

Published and unpublished data for our review were identified by searching the MEDLINE, EMBASE, PubMed, and American Society of Clinical Oncology meeting library databases up to May 2019, the ClinicalTrials.gov Web site for registered clinical trials, and references from relevant articles. Data were also derived from leading international sarcoma trials conducted by the COG and the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG). Searches included all study designs, but articles considered were limited to those written in English. The articles focused on children 0 to 14 years of age; adolescents and young adults 15–39 years of age were prioritized.

REVIEW

RMS

Classification

As of 2013, the World Health Organization system uses light microscopy to classify RMS into various histologic subtypes. The two major subtypes are aRMS and eRMS. Alveolar RMS is recognized by a characteristic alveolar pattern with nests of tumour cells separated by collagenous fibrous septa. Embryonal RMS demonstrates immature myoblastic and stellate cells and includes botryoidal and pleomorphic variants. Other less-common RMS subtypes include sclerosing or spindle-cell RMS and pleomorphic RMS[7]. Sclerosing or spindle-cell RMS in children tends to occur in the paratesticular region, followed by the head and neck—the latter associated with *MYOD1* mutations[7,8]. Pleomorphic RMS is an aggressive neoplasm with skeletal muscle differentiation that occurs in adults more than 45 years of age and that behaves biologically and clinically like other adult-type high-grade STSs[7]. Our review focuses only on non-pleomorphic RMS.

The two most common histologic subtypes, eRMS and aRMS, are found in 70% and 30% of all children with RMS and, less commonly, in adults[7]. The childhood RMS cells are derived from mesenchymal progenitor cells that fail to complete normal muscle development[7]. Embryonal RMS arises mainly from the head, neck, orbit, and genitourinary tract regions[7]. Alveolar RMS tumours are classically found within the deep tissues of the extremities[7].

Molecular and Cellular Biology

Alveolar RMS is associated with specific abnormal translocations, t(2;13)(q35;q14) or t(1;13)(p36;q14), resulting in chimeric fusion genes *PAX3–FOXO1* and *PAX7–FOXO1* in 60% and 20% of cases respectively. Another 20% of aRMS cases lack the fusion and are termed "fusion-negative aRMS." Fusion-negative aRMS has genomic profiling and clinical behaviour most resembling eRMS, with similarly better survival outcomes than those seen with fusion-positive aRMS[9]. In a very recent review[10], the authors suggested that those findings provide genetic evidence for the combination of eRMS and fusion-negative aRMS tumours into a single "fusion-negative" RMS subset.

The *PAX3/7–FOXO1* fusion gene status of RMS is a useful biomarker that predicts prognosis and is being used for risk assignment in large cooperative clinical trials through the COG[11]. Molecular investigation to detect a *FOXO1* fusion is recommended for all patients diagnosed with aRMS; acceptable techniques include fluorescence *in situ* hybridization, reverse-transcriptase polymerase chain reaction, or next-generation sequencing (specifically, RNA sequencing)[12].

Within the morphologic spectrum of sclerosing or spindle cell RMS and eRMS, recurring homozygous and heterozygous *MYOD1* Leu122Arg mutations occur, and in one third of cases, a *PIK3CA* mutation coexists[8]. Those molecular subtypes define an aggressive RMS subset with a poor clinical outcome despite multimodal chemoradiation treatment; in more than 80% of pediatric cases reviewed retrospectively, patients died of their disease[8].

Evolution of Chemotherapy and Current Standard Treatment by Risk Group

The IRSG proposed presurgical stages (1–4, depending on the anatomic location of the primary tumour) and postsurgical groupings (I–IV) that apply to surgical or pathology features, or both[10]. The COG has classified RMS into 3 risk groups (low, intermediate, and high) based on tumour location (favourable vs. unfavourable), histology (aRMS vs. eRMS), and extent of disease (distant metastases). Combination chemotherapy with VAC (vincristine–actinomycin–cyclophosphamide), together with surgery or RT (or both) has formed the backbone for treating RMS since the 1970s. It has been clear that coordinated multi-agent multimodality treatment of long duration is required for this complex tumour biology[13] (Table I).

Low-Risk Group: Low-risk disease includes localized eRMS in favourable or unfavourable sites (stages 1–3), grossly resected with or without microscopic residual disease, or resected tumour-involved regional lymph nodes, or both[22]. Patients with low-risk RMS have an estimated 5-year failure-free survival rate greater than 85%[14,23,24]. Trials have attempted to reduce toxicity by lowering the RT dose and the cumulative alkylator exposure in favourable-risk patient populations. Regardless, findings from the IRSG studies suggest that maintaining alkylator intensity is necessary to preserve survival outcomes[14,24].

The ARST0331 trial reported a failure-free survival rate of 89% using low-dose cyclophosphamide in a low-risk population treated over a shortened duration of 22 weeks (from 45 weeks), with weekly vincristine. The regimen incorporated VAC for 4 cycles (cyclophosphamide 1.2 g/m^2, total cumulative dose 4.8 g/m^2), followed by VA for 4 cycles, plus RT equivalent to that in predecessor trial D9602 and slightly reduced compared with that in IRS-IV (that is, ranging between no RT and 45 Gy according to the risk group)[15].

TABLE I Clinical trials for newly diagnosed rhabdomyosarcoma (RMS), by risk group

COG risk group	Reference (study name)	RMS type	Stage and group	Pts *(n)*	Treatment	Survival outcomes
Low risk						
	Raney *et al.*, 2011[14] (D9602)	eRMS	(A) Stage 1, group I/IIA; stage 1, group III orbit; stage 2, group I	264	(A) Vincristine–dactinomycin with or without RT[a]	5-Year failure-free survival: 89%; overall survival: 97%
			(B) Stage 1, group IIB/C; stage 1, group III non-orbit; stage 2, group II; stage 3, group I/II	78	(B) Vincristine–dactinomycin–cyclophosphamide with or without RT[a] (cdC: 28.6 g/m^2) 47 Weeks total	5-Year failure-free survival: 85%; overall survival: 93%
	Walterhouse *et al.*, 2014[15] (ARST0331)	eRMS	Stage 1/2, group I/II; or stage 1, group III orbit	271	Vincristine–dactinomycin–cyclophosphamide for 4 cycles (cdC: 4.8 g/m^2) Vincristine–dactinomycin for 4 cycles, plus RT (36–45 Gy) for group II/III 24 Weeks total	3-Year failure-free survival: 89%; 3-year overall survival: 98% Stage 1, group IIB/C, or stage 2, group II: failure-free survival, 90%; overall survival, 96%
Intermediate risk						
	Arndt *et al.*, 2009[16] (D9803)	eRMS	Stage 2/3, group III Stage 4, group IV, <10 years of age	617	(A) Vincristine–dactinomycin–cyclophosphamide (cdC: 30.8 g/m^2) plus RT	(A) vs. (B) Overall cohort: 4-Year failure-free survival, 73% vs. 68%, p=0.3
		aRMS or undifferentiated sarcoma	Nonmetastatic		(B) Vincristine–dactinomycin–cyclophosphamide alternating with vincristine–topotecan–cyclophosphamide (cdC: 25.1 g/m^2) plus RT 42 Weeks total	eRMS, group IV, <10 years of age: 4-Year failure-free survival, 64% vs. 56%, p=0.6 aRMS or undifferentiated, stage 2/3, group II/III: 4-Year failure-free survival, 68% vs. 52%, p=0.05
	Hawkins *et al.*, 2018[17] (ARST0531)	eRMS	Stage 2/3, group III	222	(A) Vincristine–dactinomycin–cyclophosphamide (cdC: 16.8 g/m^2) plus RT	(A) vs. (B) Overall cohort: 4-Year event-free survival, 63% vs. 59%, p=0.51; 4-Year overall survival, 73% vs. 72%, p=0.80
		aRMS	Stage 1–3, group I–III	226	(B) Vincristine–dactinomycin–cyclophosphamide or vincristine–irinotecan plus RT (cdC: 8.4 g/m^2) 42 Weeks total	

TABLE I Continued

COG risk group	Reference (study name)	RMS type	Stage and group	Pts *(n)*	Treatment	Survival outcomes
High risk						
	Weigel *et al.,* 2016[18] (ARST0431)	eRMS aRMS	Metastatic, all risk groups	109	Vincristine–irinotecan (weeks 1–6, 20–25, 47–52), vincristine–doxorubicin–cyclophosphamide alternating with ifosfamide–etoposide (weeks 7–19, 26–34), vincristine–dactinomycin–cyclophosphamide (weeks 38–46), RT to primary tumour (weeks 20–25) 54 Weeks total	3-Year event-free survival, 38%; overall survival: 56% No more than 1 Oberlin risk factor[b]: 3-Year event-free survival, 69%; overall survival: 79% 2 or more Oberlin risk factors[b]: 3-Year event-free survival, 20%, overall survival: 14%
	Bisogno *et al.,* 2018[19], and Bisogno *et al.,* 2019[20] (EpSSG RMS 2005)	eRMS	Incompletely resected, localized, unfavourable sites, with or without nodal involvement	484 (1st randomization)	1st randomization: ifosfamide–vincristine–dactinomycin for 9 cycles vs. ifosfamide–vincristine–dactinomycin plus doxorubicin for 4 cycles, then ifosfamide–vincristine–dactinomycin for 5 cycles	Ifosfamide–vincristine–dactinomycin without vs. with doxorubicin: 3-Year event-free survival, 63.3% vs. 67.5%, p=0.33 Standard arm vs. maintenance arm: 5-year overall survival, 73.7% vs. 86.5%, p=0.0097
		aRMS	Without nodal involvement	371 (2nd randomization)	2nd randomization: stop treatment (standard arm) vs. vinorelbine plus oral cyclophosphamide (maintenance arm) 24 Weeks total	
	Malempati *et al.,* 2019[21] (ARST08P1)	aRMS (70%) eRMS	Metastatic	168	Vincristine–irinotecan, vincristine–doxorubicin–cyclophosphamide alternating with ifosfamide–etoposide, vincristine–dactinomycin–cyclophosphamide plus cixutumumab or temozolomide, RT to primary and metastatic sites 54 Weeks total	Cixutumumab vs. temozolomide: 3-Year event-free survival, 16% vs. 18%, p=0.02; overall survival, 47% vs. 33%, p=0.03

[a] Subgroup A: 36 Gy for stage 1, group IIA; 45 Gy for stage 1, group III orbit; Subgroup B: 36 Gy for stages 2/3, group IIA.
[b] The Oberlin risk factors are age greater than 10 years or less than 1 year, unfavourable primary disease site, 3 or more metastatic sites, and bone and bone marrow involvement.
COG = Children's Oncology Group; Pts = patients; eRMS = embryonal RMS; RT = radiation therapy; cdC = cumulative dose of cyclophosphamide; aRMS = alveolar RMS.

However, the very low dose of cyclophosphamide and lower RT dose might have accounted for the inferior local failure rate compared with rates achieved in IRS-IV (8.1% vs. 2% for stage 1 group IIA, and 11.5% vs. 4% for group III orbit tumours)[14,15]. Consequently, some patients with unresected eRMS are now offered intermediate-risk therapy, as discussed next.

Intermediate-Risk Group: Randomized assessments of various combinations of chemotherapy agents in sequential IRSG, COG, and EpSSG trials failed to demonstrate superiority compared with the VAC backbone. The IRSG analyzed four consecutive trials between 1972 and 1997. In the first three IRS trials (IRS-I, IRS-II, IRS-III), the addition of doxorubicin[25,26] or doxorubicin and cisplatin with or without etoposide[23] to the VAC regime showed no benefit. The additional agents only contributed to toxicity in patients with intermediate or advanced disease. Most recently, the EpSSG confirmed that the addition of dose-intensified doxorubicin offered no benefit[19].

In the IRS-IV study, standard VAC was compared with VAI (vincristine–actinomycin–ifosfamide) or VIE (vincristine–ifosfamide–etoposide). Compared with combination multiagent therapy with ifosfamide and etoposide (VAI and VIE), VAC (cyclophosphamide at 2.2 g/m^2 per dose) was equally effective, with no significant difference in the 3-year failure-free survival rate (77%, 77%, and 75% for VAI, VIE, and VAC respectively; $p = 0.42$) or the OS rate (84%, 88%, and 84% for VAI, VIE, and VAC respectively; $p = 0.63$)[24].

In ARST0531, VAC was compared with a regimen that alternated between VAC and vincristine–irinotecan, with no difference in event-free survival [EFS (4-year EFS: 63% vs. 59%; $p = 0.51$)] or OS (73% vs. 72%, $p = 0.80$)[17]. The alternating regimen was, however, associated with a lower incidence of hematologic toxicity[17] and a potential reduction in long-term morbidity in relation to the 50% reduction in the cumulative cyclophosphamide dose (8.4 g/m^2 vs. 16.8 g/m^2). That regimen has thus been adopted as the new backbone for the newest ongoing study, ARST1431.

High-Risk Group: High-risk RMS is defined as disease with distant metastases and fusion-positive aRMS, or distant metastases in fusion-negative RMS in children more than 10 years of age[12]. The prognosis for children with high-risk RMS is poor (3-year EFS: 27%; OS: 34%)[27]. Several independent variables (the so-called Oberlin factors) for poor prognosis have been identified: age (≤1 year, ≥10 years), unfavourable site, bone or bone marrow involvement, and multiple metastases (≥3)[27]. A greater number of prognostic variables (≥2 Oberlin factors) correlate with decreased EFS.

A large cooperative pediatric trial that enrolled 109 patients was intended to improve the outcome for children with high-risk disease[18]. The protocol offered an intensive regime that incorporated vincristine–irinotecan with interval-compressed treatment involving alternating cycles of vincristine–doxorubicin–cyclophosphamide and ifosfamide–etoposide[18]. For children with metastatic disease and no more than 1 Oberlin risk factor, that intensive backbone chemotherapy improved EFS to 69% from 44% in the Oberlin cohort[27]; however, no significant benefit accrued to patients with 2 or more Oberlin risk factors (3-year EFS: 20%)[18]. Children less than 10 years of age with metastatic eRMS and no more than 1 Oberlin risk factor experience outcomes equivalent to those in intermediate-risk disease, with a 3-year EFS of 60%[18], which is comparable to the historical 4-year EFS rate of 64% with VAC alone (but with cumulative cyclophosphamide increased to 30.8 g/m^2)[16]. Recent attempts to derive benefit by adding temozolomide or blockade of insulin-like growth factor 1 with antibodies such as cixutumumab (in ARST08P1) to the standard multi-agent cytotoxic backbone in ARST0431[18] have failed to show significant activity[21]. Altogether, no efficient, standard risk-adapted therapy is currently available for patients with high-risk RMS.

Local Disease Control

Local control of RMS with surgical resection or radiation, or both, is central for improved survival. Surgical resection of the primary tumour (groups I and II) is generally recommended for better survival outcomes if clear surgical margins are feasible and can be achieved without incurring significant morbidity[24–26,28]. Traditionally, RMS is very radiosensitive, and RT was used as an early modality in the IRSG studies. Radiation therapy still has an important role in RMS when resection is incomplete or in the presence of regional or distant metastases; however, with improved risk stratification, neoadjuvant and adjuvant chemotherapy, and supportive care, trials such as CWS-91[29] and D9803[16] reduced the RT exposure in select groups. Current trials such as COG's ARST1431 (see NCT02567435 at https://ClinicalTrials.gov/) are using delayed primary excision after 9 weeks of chemotherapy to reduce the RT dose.

Maintenance Metronomic Chemotherapy

Of the 20%–30% of children with localized RMS who relapse on first-line therapy, about 10% achieve a response to salvage therapy[30]. Low-dose maintenance metronomic chemotherapy can be considered in children with a high risk of recurrence and is now integrated into the current COG trial for patients with intermediate-risk RMS, ARST1431. Maintenance chemotherapy uses combination intravenous vinorelbine 25 mg/m^2 on days 1, 8, and 15 of each cycle and continuous low-dose oral cyclophosphamide 25 mg/m^2. The angiogenic activity in RMS is inhibited by the prolonged or "metronomic" administration of low-dose vinorelbine and cyclophosphamide[31,32]. In children with relapsed or refractory RMS previously exposed to chemotherapy, the overall response rate to vinorelbine and cyclophosphamide was 38% in a small pilot study of 8 children[32] and 36% in a phase II study with 117 patients (median age: 12 years)[33]. Myelosuppression is the most frequently experienced toxicity with this combination therapy, but overall, the studies reported an acceptable toxicity profile.

Low-dose maintenance chemotherapy is associated with a survival advantage in high-risk RMS. A phase III trial conducted by the EpSSG investigated low-dose maintenance chemotherapy in children between 6 months and 21 years of age ($n = 371$) with localized RMS (N0 aRMS or incompletely resected eRMS from an unfavourable site, or N1 disease in complete remission)[20]. Children were randomized either to stop standard treatment or to receive an additional 6 months of maintenance. Maintenance chemotherapy was

associated with superior outcomes: the 3-year disease-free survival improved to 77.6% from 69.8% ($p = 0.061$), and the 5-year OS increased to 86.5% from 73.7% ($p = 0.0097$)[20]. The combination of vinorelbine and oral cyclophosphamide is feasible as a means of disease control with tolerable toxicity.

Novel Agents and New Therapeutic Approaches

Because of the predicted poor outcomes in this population, relapsed and refractory RMS has historically been the preferred setting for studies involving novel therapeutic approaches. As more is gradually learned about the mutational landscape of RMS, some aberrant signalling pathways are being identified, some of which could be actionable, such as the RAS–PI3K pathway, tyrosine kinase receptor signalling (including fibroblast growth factor receptor, epidermal growth factor receptor, and HER2), and key players in the cell cycle such as PTEN, TP53, and CDKN2A[10].

The most recent COG trial, ARST0921 (a phase II pilot study for relapsed pediatric RMS), used a backbone of vinorelbine–cyclophosphamide and randomized the addition of either bevacizumab or the mTOR (mechanistic target of rapamycin) inhibitor temsirolimus. Improved outcomes were observed in the patients receiving temsirolimus compared with those receiving bevacizumab—the 6-month EFS being 69.1% compared with 54.6%[34].

Immune checkpoint inhibitors have yet to earn a role in pediatric sarcoma in general[35], but very recent data from a phase I study of autologous HER2 chimeric antigen receptor T cell infusion for pediatric and adult patients with HER2-positive sarcoma—including RMS—look promising and suggest objective clinical benefit in some patients[36].

Non-rhabdomyosarcoma STS

Infantile Fibrosarcoma and Other NTRK *Sarcomas*

Fibrosarcoma is characterized by cellular proliferation composed of mitotically active, immature fibroblastic spindle cells arranged in sheets and fascicles. When they occur in children, they are classified in the very heterogeneous group designated nrSTS. They represent approximately 5%–10% of all diagnosed sarcomas in infants aged less than 1 year of age[37]. Overall, infantile fibrosarcoma (IFS) has a good prognosis; more than 80% of patients are cured[38].

Until recently, the standard of care was a combination of surgery and chemotherapy, given either in the neoadjuvant setting for inoperable tumours or as adjuvant treatment for resectable tumours. Chemotherapy has been reported to be fairly effective in IFS[39]. In 2010, Orbach *et al.*[38] retrospectively reported the European experience in 56 infants, concluding that conservative surgery remains the mainstay treatment for IFS. They suggested a vincristine–dactinomycin regimen as first-line chemotherapy for inoperable tumours with overall good prognosis.

The neurotrophic receptor tyrosine kinase genes *NTRK1, NTRK2,* and *NTRK3* respectively encode the TRK proteins TRKA, TRKB, and TRKC. Recurrent chromosomal fusion events involving various N-terminal partners and the C-terminal kinase domain of TRKA, B, or C have been identified in a diversity of cancers that occur in children, including IFS and various sarcomas that could now be regrouped as *NTRK*-positive STS[40,41].

A subset of childhood sarcomas that strongly resemble IFS by morphology criteria (IFS-like sarcomas) indeed harbour recurrent chromosomal abnormalities different from the one classically found in IFS (*ETV6–NTRK3*), including *EML4–NTRK3* fusions and rearrangements of the kinase gene *NTRK1*. Interestingly, most IFS-like sarcomas occur in infants, but some present in children of older age, with a predilection for intra-abdominal sites. Clinical outcome is less predictable, with some cases showing aggressive clinical behaviour, including distant metastases[42].

Fusions involving TRK lead to overexpression of the chimeric protein, resulting in constitutively active, ligand-independent downstream signalling. Targeted therapy with larotrectinib, a selective NTRK inhibitor, has been administered in patients with advanced-stage IFS with very promising results in studies that were developed upfront as pediatric and adult phase I studies, with an appropriate liquid formulation of the drug[43–45].

Larotrectinib is now approved by the U.S. Food and Drug Administration and the European Medicines Agency for solid tumours with *NTRK* gene fusions, with a tissue-agnostic indication. Overall management of IFS and other *NTRK*-positive STSs—specifically the role of surgery—will certainly be affected by that targeted agent.

Synovial Sarcomas

Synovial sarcoma is a malignant mesenchymal tumour with a predilection for the distal extremities[46]. It is the most common nrSTS in children and adolescents, and accounts for 5%–10% of all STS[1]. Diagnosis is confirmed by the characteristic translocation t(X;18)(p11;q11), resulting in chimeric fusion gene *SS18–SSX1, SS18–SSX2,* or rarely, *SS18–SSX4*[47]. Progression-free survival and OS outcomes have been evaluated using various criteria, response categories, and follow-up[48]. Ferrari *et al.*[49] reported an upfront 5-year EFS of 80.7% and an OS of 90.7% for localized disease in young people treated with multimodal therapy including ifosfamide–doxorubicin and RT, based on risk stratification. For young patients with low-risk (completely resected, ≤5 cm tumour), intermediate-risk (completely resected, >5 cm), and high-risk disease (unresected tumour), the 3-year EFS rates were 91.7%, 91.2%, 77.3%, and the 3-year OS rates were 100%, 100%, and 94.3% respectively[49]. Metastatic synovial sarcoma is associated with a poor prognosis, with a reported 5-year OS of 13%[50]. Prognostic variables that improve the likelihood of a second complete response with aggressive second-line therapy include an extremity primary, age at diagnosis less than 12 years, absence of chemotherapy and RT as initial treatment, and local relapse[51]. Orbach *et al.*[52] showed that a high genomic index or acquired genomic instability[53] (more prevalent in adults) predicts a greater likelihood for the tumour to metastasize, but does not reflect chemosensitivity.

No standardized treatment or consensus guidelines have been published for children and adolescents with synovial sarcoma. Several large retrospective series failed to report the routine use of chemotherapy in synovial sarcoma, with treatment modalities focused on surgery and RT[46,54,55]. More recently, the EpSSG and COG have shown in prospective analyses that surgery alone is associated with favourable outcomes in pediatric patients with localized,

completely resected small tumours (≤5 cm) regardless of histologic grade (90% EFS, 100% OS)[56], defining the standard treatment for low-risk disease[49,56,57]. Typically, for children and adolescents with localized, resectable disease, we favour surgery when feasible. To facilitate surgical resection in cases of large, deep, unresectable tumours, we adopt a multimodal approach that might include neoadjuvant RT or chemotherapy (or both), considering long-term morbidity.

Younger age in synovial sarcoma has been associated with better survival outcomes[58], but the evidence for adjuvant chemotherapy in younger patients is conflicting. Traditionally, adjuvant chemotherapy has preferentially been given to children rather than to adults[59], but the 5-year metastasis-free survival rates for children less than 17 years of age were similar whether they received chemotherapy after macroscopic resection or not (67.5% vs. 75% respectively)[59]. Other studies found no significant benefit of chemotherapy for localized disease, but a trend toward better survival for patients less than 18 years of age compared with adults[60]. Vlenterie *et al.*[55] support a significant survival advantage, independent of treatment, for children compared with older adults having localized synovial sarcoma.

Synovial sarcoma appears to be relatively more "chemosensitive" than other histologic types of STS in adults[61]. In a phase III randomized controlled trial that enrolled participants 18–60 years of age with locally advanced, unresectable, or metastatic mixed-histology STS (10%–20% being synovial sarcoma), overall response was better (Response Evaluation Criteria in Solid Tumors, ver. 1.0), 26% vs. 14%, for combination doxorubicin–ifosfamide compared with doxorubicin alone, but no survival advantage accrued (median OS: 14.3 months vs. 12.8 months; $p = 0.076$)[62]. Trabectedin has shown promising results in retrospective trials[63,64] by blocking transcription factors and affecting tumour macrophages[65]. In a multicentre retrospective trial involving 61 patients 18–68 years of age diagnosed with the highest-risk synovial sarcoma (metastatic disease and heavily pretreated), trabectedin was associated with an objective response rate of 15%, with 35% of the remaining patients achieving disease stabilization[63].

Immunotherapeutic strategies are in development, including those targeting synovial sarcoma that expresses New York esophageal squamous cell carcinoma (NY-ESO-1), a cancer/testis antigen[66]. The NY-ESO-1 antigen is not typically found in normal tissues, but it is expressed within several tumour types, including synovial sarcoma, with up to 80% frequency[67]. It can induce a cellular immune response and acts as a target for immunotherapy[68]. Using engineered T cells targeting NY-ESO-1, D'Angelo *et al.*[69] reported an antitumour response over several months in 6 of 12 patients with metastatic synovial sarcoma (50%). In that therapy, autologous T cells were genetically modified or transduced with NY-ESO-1 T-cell receptors and were re-infused into patients to target tumour-specific NY-ESO-1. The results from ongoing trials of such cellular therapies and vaccines are awaited (see NCT01343043, NCT03250325, NCT02869217, and NCT03450122 at https://ClinicalTrials.gov/).

BCOR-*Rearranged and* CIC-*Rearranged Sarcomas*

Ewing sarcoma is a highly aggressive tumour, most frequently arising from bone, but also from soft tissue in approximately 10% of cases[70]. Ewing-like sarcomas are a heterogeneous group of small round-cell sarcomas that, histologically and clinically, are subtly different from Ewing sarcoma.

CIC-rearranged tumours are the most frequent of the Ewing-like sarcomas, comprising up to two thirds of *EWSR1*-negative Ewing-like tumours[71]. Interestingly, these sarcomas present as soft-tissue tumours in a large proportion of cases (87%) and share some immunohistochemical features with Ewing sarcoma (strong CD99 expression), with some more-specific features (ETV4 and WT1 expression)[70]. Molecular testing to validate a *CIC* rearrangement is obviously necessary to confirm the diagnosis. From a clinical perspective, these tumours most commonly present in the extremities of young adult patients[72], and they are believed to have a more aggressive course than that observed in classic Ewing sarcoma. Responses to neoadjuvant chemotherapy have been described as modest and often transient, with frequent subsequent tumour progression. For patients with localized disease, the current question is whether a focus on definitive local control, in an "adult soft-tissue sarcoma approach," should therefore be favoured[73]. The largest cohort of *CIC*-rearranged tumours so far (115 cases) was published by Antonescu and colleagues[72], who confirmed the pivotal role of local control and the aggressive clinical course of these tumours, 5-year survival being 43%.

BCOR-rearranged round-cell sarcomas represent the second-most-frequent subclass of Ewing-like sarcoma and offer another very different clinical picture. Estimates of the prevalence of *BCOR*-rearranged sarcoma range from 4% to 14% of all cases of undifferentiated unclassified sarcoma[74,75]. Interestingly, in approximately one third of cases, they also present as soft-tissue tumours more frequently than do "classical" Ewing sarcomas[70]. Of all *BCOR*-rearranged sarcomas, 60% harbour *BCOR–CCNB3* fusions[71]. Molecular confirmation of the *BCOR* rearrangement through reverse-transcriptase polymerase chain reaction or RNA sequencing has become a critical diagnostic test, because the morphologic and immunohistochemical features show considerable overlap with classical Ewing sarcoma and with other subtypes of small round-cell tumours, lymphomas, and carcinomas that can also arise in soft tissue[73]. This type of tumour seems to occur frequently in male adolescents and young adults[76,77]. Compared with *CIC*-rearranged tumours, *BCOR*-rearranged tumours appear to be sensitive to chemotherapy agents used in the treatment of classical Ewing sarcoma (vincristine, doxorubicin, cyclophosphamide–ifosfamide, etoposide) and have a comparable prognosis[76,77]. Until additional prospective data from larger studies are available, clinicians might be inclined to continue with Ewing sarcoma–like practices: neoadjuvant multi-agent chemotherapy, with assessment of chemosensitivity, appropriate local control, and further adjuvant chemotherapy[73].

DSRCT

The rare, highly aggressive DSRCT usually presents in young men as diffuse peritoneal or abdominopelvic disease. Occasionally, extra-abdominal disease is also noted. These tumours are characterized histologically by nests of

undifferentiated small round blue cells, lying within abundant desmoplastic stroma[78]. They are distinguished by the reciprocal chromosomal translocation t(11;22)(p13;q12) that results in the fusion of *EWSR1* with *WT1*[78]. Prognosis is dismal, with a 5-year OS of 18%[79]. Management of DSRCT is challenging, and advancements in the care of children have been limited by the rarity of the tumour.

Desmoplastic small round-cell tumours are transiently responsive to regimens typically used for Ewing sarcoma, including vincristine–doxorubicin–cyclophosphamide or ifosfamide–etoposide, often implemented in the first line[80]. Other second-line systemic options include combinations of alkylating agents and topoisomerase-containing regimens, including temozolomide–irinotecan, cyclophosphamide–topotecan, and high-dose ifosfamide, with no superior strategy[80,81]. Recently, metronomic therapy was investigated for DSRCT, with encouraging results[80].

Cytoreductive surgery and consolidative RT within a centralized care setting[82] are critical for any chance of disease control. After a first report of complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy with cisplatin for children with DSRCT in 2007[83], Hayes-Jordan and colleagues[84] more recently reported a median OS of 31 months compared with 7 months for 50 children (21 with DSRCT) after complete or incomplete cytoreduction. The same authors also demonstrated improved short-term survival for select patients with DSRCT (n = 14) who had complete cytoreductive surgery (median OS: 58 months; 3-year OS: 79%)[85]. Despite local peritoneal control, 33% of patients still developed distant disease, emphasizing the importance of systemic therapy. Surgery followed by consolidative whole abdominopelvic RT should also be considered[86].

Because of a better understanding of DSRCT genomics and the poor outcomes with current therapies, novel agents are being developed within pediatrics to target downstream targets of the *EWS–WT1* fusion protein. Those agents include the inhibitor drug prexasertib[87], which targets checkpoint kinase 1 *(CHK1)*, leading to DNA damage; use of ONC201[88], which induces apoptosis through the TRAIL pathway and which is showing success in preclinical models; tolerability of mTOR inhibitor regimes[89]; and activity with trabectedin[90], eribulin[91], and pazopanib[92].

Collaborative Systemic Approach for Children and Adults

Pediatric oncology facilitates centralized care for children and adolescents with sarcoma within specialized centres and has established a high degree of international collaboration to ensure greater access to large cooperative clinical trials and adherence to treatment protocols. Bidirectional education between providers caring for adults with "pediatric-type" sarcomas is mandatory to ensure that standards of care are being discussed in multidisciplinary settings. Pediatric cooperative groups are endeavoring to enrol adolescents and young adults onto pediatric-based clinical trials by increasing the upper limit of eligibility to 50 years of age[93,94]. Europe will be opening a multi-arm, multi-stage study (FaR-RMS) for all ages of children and adults with localized and metastatic frontline and relapsed RMS to explore treatment for RMS that will incorporate molecular risk stratification[95]. The pragmatic aspects of delivering "'pediatric-type" therapy to adults require additional discussion, but intention-to-treat is an important beginning. Similarly, with the rapid introduction of targeted agents and immunotherapies in adult trials, further opportunities are arising for collaborations that will ensure equal access to, and evaluation of, novel therapeutic strategies for patients of all ages with rare sarcomas[96].

SUMMARY

In this review, we highlighted the pivotal role of systemic therapy in the treatment of RMS. The VAC backbone remains standard, but the addition of maintenance therapy is offering an intriguing signal. Local therapy with surgery or RT, or both, is still crucial for these tumours, and international collaborative work has achieved appropriate risk stratification to spare patients the use of chemotherapy or RT whenever possible. Relapsed and locally advanced or metastatic disease remains a challenge both for RMS and for other STSs such as synovial sarcoma and DSRCT. The hope is that molecular characterization and new therapies will help to treat STS in children, as has been seen with the ground-breaking use of larotrectinib for tumours with *NTRK* fusions. The additional work needed for improving outcomes in STS is widely acknowledged; however, the rarity of the tumours and their aggressive clinical course in children poses challenges in conducting clinical trials. Future international collaborations for children and adults, such as the EpSSG frontline and relapsed RMS trial, are needed to move forward.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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