REVIEW

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Molecular targeted therapies for pediatric atypical teratoid/rhabdoid tumors

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ABSTRACT
Atypical teratoid/rhabdoid tumors (AT/RTs) are lethal central nervous system tumors, which are primarily diagnosed in infants. Current treatments for AT/RTs include surgery, radiotherapy, and chemotherapy; these treatments have poor prognoses and challenging side effects. The pivotal genetic event in AT/RT pathogenesis comprises the inactivation of *SMARCB1* or *SMARCA4*. Recent epigenetic studies have demonstrated mutual and subtype-specific epigenetic derangements that drive tumorigenesis; the exploitation of these potential targets might improve the dismal treatment outcomes of AT/RTs. This review aims to summarize the literature concerning targeted molecular therapies for pediatric AT/RTs.

KEYWORDS
Atypical teratoid/rhabdoid tumors, *SMARCB1*, *SMARCA4*, SWI/SNF complex, Targeted molecular therapy

INTRODUCTION

Atypical teratoid/rhabdoid tumors (AT/RTs) in the central nervous system (CNS) are rare and highly aggressive malignancies that tend to occur in infants aged ≤3 years; such tumors are considered grade 4 in the 2021 World Health Organization Classification of CNS tumors.[1] Current treatment strategies involve intensive multimodality therapies that include surgery, intrathecal and systemic chemotherapy, and radiotherapy; these strategies offer moderate survival improvements but carry the risk of significant treatment-related morbidities.[2,3]

The genetic landscape of AT/RTs is surprisingly simple: few landmark discoveries have been reported since Sévenet et al.[4] initially reported mutations of the *INI1* (*SMARCB1*) gene in 1999. The genetic hallmark of AT/RTs comprises the inactivation of the *SMARCB1* locus at 22q11.2. In rare cases, SMARCB1 protein expression is intact in neoplasms with AT/RT features; such neoplasms exhibit inactivation of the *SMARCA4* locus at 19p13.[5–7] As key components of the SWI/SNF chromatin remodeling complex, SMARCB1 and SMARCA4 have been identified in various extracranial tumors (e.g., pediatric malignant RTs and renal medullary carcinoma).[8] SMARCB1 is the most commonly inactivated SWI/SNF complex subunit in mesenchymal neoplasms, while the inactivation of SMARCA4 has been associated with a greater frequency of germline mutations.[9] Although the specific mechanisms by which *SMARCB1* and *SMARCA4* contribute to AT/RT pathogenesis remain poorly understood, multiple investigations of targeted drugs

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have been inspired by the various pathways and epigenetic deregulation events that result from these simple genetic inactivations.[10,11]

Considering the rapid development of novel technologies and rapid advances in epigenetics knowledge, this review summarizes recent research concerning targeted therapy for pediatric AT/RTs.

CURRENT CLINICAL MANAGEMENT OF AT/RTs

Despite improvements related to the use of aggressive and multimodal therapies during the past decade, survival rates remain poor among patients with AT/RTs. As shown in Table 1, multimodal therapies currently include surgery, chemotherapy (e.g., high-dose chemotherapy [HDC] with peripheral blood stem cell rescue and intrathecal chemotherapy [IT]), radiotherapy, and prompt treatment strategies for specific stages of the disease. Thus far, there is no consensus or standard protocol concerning treatment for AT/RTs.

The survival outcomes of gross total resection (GTR) have varied among studies. A recent study by Richards et al.[12] demonstrated better survival in the complete total resection group than in the subtotal resection group. A national retrospective study by Lafay-Cousin et al.[13] showed similarly favorable results; 2-year overall survival (OS) was 60% ± 12.6% in the GTR group. However, other multimodal treatment trials have indicated that GTR does not significantly improve patient prognosis.[2,3,14] Maximal-safe resection and second-look surgery are recommended as components of multimodal treatment in these trials. However, long-term outcomes cannot be improved solely by increasing the rate of GTR.

Innovations in chemotherapy dose intensity and strategy have gradually improved survival rates among patients with AT/RTs. Slavc et al.[15] proposed an altered chemotherapy regimen, consisting of three 9-week courses of a dose-dense regimen including doxorubicin, cyclophosphamide, vincristine, ifosfamide, cisplatin, and etoposide followed by IT with methotrexate, HDC, and local radiotherapy to treat patients with AT/RTs. This strategy delayed the requirement for radiotherapy in all nine included patients; the 5-year OS was 100% and the 5-year event-free survival (EFS) was 88.9% ± 10.5%. Additionally, based on the chemotherapy regimen in Children's Oncology Group (COG) 99703, the recent clinical trial COG ACNS0333 added methotrexate and HDC during induction and post-induction chemotherapy.[3] This therapy improved survival (4-year EFS 35%) compared with the historical therapies (4-year EFS 6.4%).[3] Conversely, a regimen that involved high-dose methotrexate-based induction and myeloablative HDC demonstrated poor outcomes: the 3-year EFS was 21% ± 9% and the 3-year OS was 26% ± 10%.[16] For patients aged <3 years, chemotherapy that includes HDC with autologous stem cell rescue is considered the main component of multimodal treatment.

The young age of patients with AT/RTs makes radiotherapy challenging: early radiotherapy offers a better prognosis but carries a significant risk of leukoencephalopathy or radiation necrosis, while delayed radiotherapy carries a lower risk of severe CNS complications but tends to allow disease progression.[17] Additionally, the outcomes of radiotherapy strategies have considerably differed among studies. Some studies have reported a tendency to relapse among patients who receive delayed radiotherapy.[18–20] Other studies reported that the risks of delayed radiotherapy were negligible among patients who received tailored regimens.[3,21,22]

After extensive explorations of optimal treatment strategies, survival outcomes have substantially improved among patients with AT/RTs. However, the median OS of patients with AT/RTs is <18 months. Novel therapies are required for patients with AT/RTs, particularly among younger patients and patients with M+ stage tumors.

MOLECULAR PATHOGENESIS OF AT/RTs

Epigenetic dysregulation: Chromatin remodeling

The inactivation of *SMARCB1* or *SMARCA4* in AT/RTs results in the loss of their protein products, which are core subunits of the SWI/SNF complex. The SWI/SNF chromatin remodeling complex modifies nucleosome position, thus regulating gene expression through ATP-dependent physical alteration of the chromatin conformation.[23] The SWI/SNF complexes contain two main units named Brahma/SWI2-related gene 1/Brahma-associated factor (BAF) and polybromo-associated BAF.[24] SMARCB1 is a pivotal subunit of BAF that stabilizes the SWI/SNF complex, thus enabling SWI/SNF to bind to the typical enhancer. Therefore, the loss of SMARCB1 results in the presence of fewer SWI/SNF complexes, reducing the affinity of SWI/SNF for chromatin and preventing the maintenance of normal enhancer function.[25,26] Alver et al.[27] reported that reintroduction of SMARCB1 to SMARCB1-knockout cell lines led to widespread recruitment of the SWI/SNF complex to previously unoccupied enhancers, along with activation of these enhancers, and resolution of promoter bivalency toward an active state. Furthermore, Nakayama et al.[28] found that SMARCB1 rescue in AT/RTs resulted in increased genome-wide BAF complex occupancy, thereby facilitating widespread enhancer activation. Although the specific functions of SMARCA4 in AT/RTs remain unclear because *SMARCA4* mutations are rare, Moreno et al.[29] found that the

TABLE 1 Latest clinical trials using chemotherapy and radiotherapy for pediatric patients with atypical teratoid/rhabdoid tumors

Reference	Time	Age (years)	M+, *n*	Surgery	Chemotherapy	Radiotherapy	Outcome	Conclusion
Reddy, 2020[3]	2008–2017	<3 ($n = 54$) ≥3 ($n = 11$)	24	GTR ($n = 25$) NTR ($n = 11$) Subtotal, partial, or biopsy ($n = 29$)	ACNS0333 chemotherapy regimen ($n = 65$)	Focal radiation ($n = 28$) CSI ($n = 6$)	4-year EFS 37% 4-year OS 43%	ACNS0333 regimen improved survival compared with historical therapies for AT/RTs
Yamasaki, 2019[21]	2005–2016	<3 ($n = 31$) ≥3 ($n = 7$)	23	GTR ($n = 9$) Biopsy ($n = 6$)	Non-anthracycline-based regimen ($n = 18$) Anthracycline-based regimen ($n = 16$) HDC ($n = 19$)	CSI plus local ($n = 12$) Local ($n = 8$) whole brain plus local ($n = 1$)	2-year OS 66.6% ± 8.3% 2-year PFS 45.9% ± 8.7% 5-year OS 44.2% ± 9.9% 5-year PFS 34.2% ± 8.9%	Multimodal therapy improved outcomes mainly in M0 patients CSI did not improve the prognosis
Park, 2021[22]	2005–2016	<3 ($n = 43$)	16	GTR ($n = 24$) Subtotal resection ($n = 18$) Biopsy ($n = 1$)	KSPNO-S052/-S082 ($n = 18$) KSPNO-S1101 ($n = 24$)	Early adjuvant local RT ($n = 14$) Salvage local RT at relapse /progression ($n = 13$) CSI at 3 years old ($n = 2$)	KSPNO-S052/-S082: 3-year PFS 0% KSPNO-S1101: 3-year PFS 47.4%	Early adjuvant RT and HDC improve outcomes of AT/RTs
Upadhyaya, 2021[73]	SJYC07: 2007–2017 SJMB03: 2003–2013	<3 ($n = 52$) ≥3 ($n = 22$)	24	Maximal safe surgical resection ($n = 74$)	SJYC07-IR ($n = 34$) SJYC07-HR ($n = 18$)	SJMB03-AR (23.4 Gy CSI) ($n = 11$) SJMB03-HR (36–39.6 Gy CSI) ($n = 11$)	SJYC07-IR: 5-year PFS 31.4% ± 9.2%; OS 43.9% ± 9.5% SJYC07-HR: 5-year PFS and OS 0% SJMB03-AR: 5-year PFS 72.7% ± 12.7%; OS 81.8% ± 11% SJMB03-HR: 5-year PFS and OS 18.2% ± 9.5%	Post-operative CSI and adjuvant chemotherapy improved outcomes in children with non-metastatic AT/RTs
Mousa, 2021[74]	1996–2013	<3 ($n = 30$) ≥3 ($n = 13$)	17	GTR ($n = 14$) Subtotal resection ($n = 23$) Biopsy ($n = 6$)	Malignant rhabdoid tumor protocol ($n = 23$) Rhabdomyosarcoma protocol ($n = 3$) Baby brain protocol ($n = 1$) VAC protocol ($n = 1$) VAIA pcrotocol ($n = 1$)	CSI then focal boost ($n = 10$) Focal irradiation ($n = 7$) Palliative irradiation ($n = 1$)	Median OS time: 16.9 months 2-year OS 41.9% ± 9.6% 5-year OS 27.9% ± 9.2%	Postoperative RT and aggressive trimodal therapy are associated with improvement in median survival

Abbreviations: AT/RTs, atypical teratoid/rhabdoid tumors; SJYC07, St. Jude Young Children 07; SJMB03, St. Jude Medulloblastoma 03; IR, intermediate risk; AR, average risk; HR, high risk; GTR, gross total resection; NTR, near-total resection; CSI, craniospinal irradiation; EFS, event-free survival; OS, overall survival; PFS, progression-free survival; HDC, high dose chemotherapy; KSPNO: Korean Society for Pediatric Neuro-Oncology; VAC, vincristine, actinomycin-D, and cyclophosphamide; VAIA, vincristine, adriamycin, ifosfamide, actinomycin-D; RT, radiotherapy.

deletion of *SMARCA4* in cerebellar granule cell precursors led to severe proliferation deficits in those cells, along with a hypoplastic cerebellum. SMARCA4 has similar pro-proliferative functions in the chromatin remodeling complexes of embryonic stem cells.[30] The mechanisms underlying the dramatic cell proliferation and differentiation consequences related to the loss of SMARCB1 or SMARCA4 in SWI/SNF complexes might involve histone modifications.

Epigenetic dysregulation: Histone modification

Global alterations in covalent histone-tail modifications (e.g., acetylation, methylation, and phosphorylation) are frequently observed in cancer, along with aberrant expression patterns of enzymes that mediate these reactions. SWI/SNF complexes can interact with p300 to modulate histone H3 lysine 27 acetylation (H3K27ac), a chromatin marker associated with active chromatin organization and gene transcription; therefore, the loss of SMARCB1 leads to reduced acetylation of H3K27.[25] In AT/RT cell lines, Wang et al.[25] demonstrated that H3K27ac is decreased around specific enhancers that are necessary to control the expression patterns of genes linked to developmental processes. Additionally, the activities of polycomb repressive complex 2 (PRC2) and SWI/SNF are reportedly balanced by distinct modifications of H3K27.[23] PRC2 is the only mammalian enzyme known to catalyze the methylation of H3K27; it mainly functions through the enhancer of zeste homolog 2 (EZH2) methylase subunit.[31] Among the methylation products of PRC2, H3K27 trimethylation (H3K27me3) tends to overlap with the absence of H3K27ac in AT/RTs.[32] Furthermore, ChIP-seq analysis revealed co-localization of SMARCA4 and EZH2, which indicates that reduced SMARCA4 activity will lead to increased H3K27me3 and loss of activity among genes that depend on EZH2.[5]

Epigenetic dysregulation: DNA methylation

The 2021 World Health Organization Classification of CNS Tumors introduced molecular diagnostic criteria into the definitions of AT/RTs, in response to the extensive evidence that specific assortments of molecular alterations have prognostic value and can be used to define distinct tumor types. In 2016, Torchia et al.[33] analyzed primary AT/RT tissues and cell lines to characterize the genomic and epigenomic landscapes of AT/RTs. Genome-wide methylation profiling and RNA sequencing data in subsequent studies have revealed the existence of three molecular subtypes: Notch/sonic hedgehog (ATRT-SHH), tyrosinase enzyme (ATRT-TYR), and *MYC* oncogene (ATRT-MYC).[33,34]

Ho et al.[35] reanalyzed published methylation array profiles and provided an overview of the molecular characteristics of each AT/RT subtype. The ATRT-SHH subtype (Group 1 in the work by Torchia et al.[33]) overexpresses components of the Notch and sonic hedgehog pathways. Gene set enrichment analyses revealed that ATRT-SHH is mainly a neuronally differentiated subtype. DNA methylation analyses suggested that the ATRT-SHH subtype could be further stratified according to a mainly supratentorial location (ATRT-SHH-1) or a mainly infratentorial (ATRT-SHH-2) location; tumors in both locations express marker genes from the Notch and SHH pathways. The ATRT-TYR subtype overexpressed tyrosinase, which is essential for neural tube development.[36,37] Gene set enrichment analysis confirmed that the melanosomal pathway and tyrosine metabolism are enriched in the ATRT-TYR subtype. DNA methylation analyses demonstrated that cribriform neuroectodermal tumors exhibited features similar to ATRT-TYR, suggesting a possible common origin for these two distinct diseases.[38] The ATRT-MYC subtype exhibits excessive activation of the *MYC* pathway. The median age is significantly higher among patients with ATRT-MYC than among patients with the other subtypes of AT/RTs. Besides, most adult AT/RTs found to belong to the ATRT-MYC subgroup and further clinical and molecular heterogeneity in ATRT-MYC may be revealed.[39,40] Using both *in vitro* and *in vivo* data, Alimova et al.[41] showed that the c-MYC oncogene is a critical regulator of malignant behavior in SMARCB1-deficient AT/RTs. A recent study demonstrated that ATRT-MYC is susceptible to glutamine metabolic inhibition with 6-diazo-5-oxo-norleucine (DON) therapy; this approach inhibits glutamine-dependent synthesis of glutathione and synergizes with carboplatin to extend survival in orthotopic mouse models with ATRT-MYC.[42] The ATRT-SHH subtype reportedly exhibits minimal overlap of enriched gene sets with ATRT-TYR and ATRT-MYC subtypes, whereas there is some overlap between ATRT-TYR and ATRT-MYC (particularly among immune response genes). Additional DNA methylation profile and transcriptomics analysis have indicated that AT/RTs with SMARCA4 inactivation form a subtype that is distinct from the above three subtypes.[6]

Other signaling pathways

Nuclear export signaling

As a critical mechanism in both tumor and normal tissues, macromolecule transport between the cytoplasm and nucleus offers a novel perspective for AT/RT treatment. The nuclear export of proteins that involves interactions of nuclear export signals with XPO1 is well-known and widely used in targeted therapy research.[43] XPO1 mediates cell proliferation through the mislocalization of tumor suppressors and stabilization of nuclear and chromosomal structures in tumor cells. Investigations of XPO1 inhibitors

have focused on a wide range of cancers, from glioblastoma to pediatric solid tumors.[44,45]

Pathak et al.[46] found an unusual cytoplasmic distribution of C-terminally truncated SMARCB1 in AT/RTs. Subsequently, they generated green fluorescent protein fusions of SMARCB1 truncating mutation along with a p.L266A mutation, which has been shown to disrupt the interaction of SMARCB1 nuclear export signals with XPO1. While SMARCB1 with the truncating mutation was localized to the cytoplasm, the double mutant version of SMARCB1 remained in the nucleus; this result indicated that nuclear export signals are required for the cytoplasmic localization of SMARCB1.[46,47] Furthermore, morphological observations and senescence-associated β-galactosidase assays showed that cells with nuclear SMARCB1 were able to become senescent, while cells with cytoplasmic SMARCB1 were not.[46] Thus, selective nuclear export signal inhibitors may be useful as targeted therapy for AT/RTs through their ability to prevent cytoplasmic localization of SMARCB1.

Human endogenous retrovirus K

HML-2 is a subtype of human endogenous retrovirus K, a repetitive element dispersed throughout the human genome that encodes several intact viral proteins with roles in stem cell maintenance and tumorigenesis.[48] After *SMARCB1* knockdown in neural stem cells, Doucet-O'Hare et al.[49] found changes in HML-2 env expression in both intracellular and extracellular fractions in AT/RT cell lines; such changes were also present in most AT/RT patient tissues. They also found that SMARCB1 binds a location adjacent to the HML-2 promoter; the restoration of SMARCB1 expression in AT/RT cell lines led to corresponding downregulation of HML-2 expression. Furthermore, targeted downregulation of HML-2 transcription by CRISPR-dCas9-binding repressor proteins led to cellular dispersion, reduced proliferation, and cell death. Finally, *HML-2* knockdown led to significant downregulation of *Ras* expression, suggesting that HML-2 regulates MAPK/ERK signaling in AT/RT cells.[49] These findings have established a clear connection between AT/RT pathogenesis and the regulation of endogenous retroviral elements; HML-2 offers another promising therapeutic target.

MOLECULAR TARGETED THERAPIES OF AT/RTS

For many decades, there was minimal progress regarding targeted therapies for AT/RTs; however, clinical trials involving AT/RT patients have shown significant advances in the past 5 years.

Mechanisms of targeted therapies

Chromatin remodeling and histone modification

As mentioned in a previous section, SWI/SNF-mediated histone modifications are critical in AT/RT pathogenesis.[50] Specifically, the acetylation statuses of downstream histones are controlled by histone acetyltransferases and histone deacetylases (HDACs). Histone acetylation presents effective targets for AT/RTs. Kerl et al.[51] reported that the HDAC inhibitor suberoylanilide hydroxamic acid (SAHA or vorinostat) functioned in a synergistic manner with fenretinide, tamoxifen, and doxorubicin; these effects were confirmed in proliferation assays, apoptosis detection assays, cell cycle analysis, and RNA expression analysis. Further assessments of SAHA in xenograft models revealed that it was an efficient radiosensitizer. Two phase 1 trials using HDAC inhibitor to treat patients with refractory tumors has been completed (Table 2, NCT00217412 and NCt01076530). Other HDAC inhibitors (e.g., panobinostat [LBH589] and resminostat) also have shown favorable pharmacokinetic and pharmacodynamic properties, which might be suitable for treatments in younger children.[52,53] For example, Muscat et al.[54] observed terminal differentiation and reduction of the self-renewal ability of malignant RT cells during low-dose panobinostat treatment; this finding was the foundation for a phase 2 trial that is currently recruiting both malignant RT and AT/RT patients (Table 3, NCT04897880). The antagonistic association between SWI/SNF and the PRC2 has an important role in AT/RT pathogenesis, through the regulation of downstream EZH2 and H3K27.[23] Gene enrichment score analysis showed that a set of H3K27 and EZH2 target genes originated from embryonic stem cells were negatively enriched in RTs, compared with normal brain tissue.[55] During *in vitro* analysis, Unland et al.[56] employed an antagonist for EZH2, 3-deazaneplanocin A (DZNep), alone and in combination with other anticancer drugs (e.g., doxorubicin) or epigenetically active compounds such as the methylation inhibitor 5-AZA-2'-deoxycytidine (5-Aza-CdR) or the HDAC inhibitor SAHA. Proliferation assays in RT cell lines demonstrated that DZNep functioned in a synergistic manner with etoposide, 5-Aza-CdR, and SAHA in terms of antiproliferative function. In a xenograft model, treatment of EZH2-mutant xenografts with tazemetostat (EPZ-6438) caused dose-dependent inhibition of tumor growth, including complete and sustained tumor regression with a corresponding reduction in H3K27me3 levels in both tumors and normal tissues.[57] An EZH2 inhibitor was beneficial in the treatment of RT xenograft models. This inspired the following clinical experiments using EZH2 inhibitors. In a phase 1 trial that involved refractory non-Hodgkin lymphoma and advanced solid tumor patients, a complete response was achieved in the first RT patient enrolled.[58] A Phase 2 trial is also ongoing (NCT03213665). One clinical trial of

TABLE 2 Closed clinical trials of targeted therapy involving patients with atypical teratoid/rhabdoid tumors

Title and trial ID	Status	Phase	Target drug involved	Molecular mechanism	Starting date
SCH 66336 in treating children with recurrent or progressive brain tumors (NCT00015899)[75]	Completed	Phase 1	Lonafarnib	Farnesyltransferase inhibitor	Jan 1, 2002
Radiolabeled monoclonal antibody therapy in treating patients with refractory, recurrent, or advanced CNS or leptomeningeal cancer (NCT00089245)	Active, not recruiting	Phase 1	^{131}I-omburtamab	Anti-GD2	July 1, 2004
Lenalidomide in treating young patients with recurrent, progressive, or refractory CNS tumors (NCT00100880)[76]	Completed	Phase 1	Lenalidomide	Immune modulation	Nov 1, 2004
Vorinostat with or without isotretinoin in treating young patients with recurrent or refractory solid tumors, lymphoma, or leukemia (NCT00217412)	Completed	Phase 1	Vorinostat	Histone deacetylase inhibitor	Aug 1, 2005
Talabostat combined with temozolomide or carboplatin in treating young patients with relapsed or refractory brain tumors or other solid tumors (NCT00303940)[77]	Completed	Phase 1	Talabostat mesylate	Dipeptidyl peptidase inhibitor	Dec 1, 2005
AZD2171 in treating young patients with recurrent, progressive, or refractory primary CNS tumors (NCT00326664)[78]	Completed	Phase 1	Cediranib maleate	VEGF receptor tyrosine kinases inhibitor	Mar 1, 2006
MK0752 in treating young patients with recurrent or refractory CNS cancer (NCT00572182)[79]	Terminated	Phase 1	MK-0752	γ-Secretase inhibitor	Jul 1, 2008
Dasatinib, ifosfamide, carboplatin, and etoposide in treating young patients with metastatic or recurrent malignant solid tumors (NCT00788125)	Active, not recruiting	Phase 1/2	Dasatinib	Growth factor receptors inhibitor	Sep 3, 2008
Veliparib (ABT-888) and temozolomide in treating young patients with recurrent or refractory CNS tumors (NCT00946335)[80]	Completed	Phase 1	Veliparib	Poly(ADP-ribose) polymerase inhibitor	Jul 1, 2009
Vorinostat and temozolomide in treating young patients with relapsed or refractory primary brain tumors or spinal cord tumors (NCT01076530)[81]	Completed	Phase 1	Vorinostat	Histone deacetylase inhibitor	Feb 1, 2010
Gamma-Secretase inhibitor RO4929097 in treating young patients with relapsed or refractory solid tumors, CNS tumors, lymphoma, or T-Cell leukemia (NCT01088763)	Terminated	Phase 1	RO4929097	γ-Secretase inhibitor	Mar 1, 2010
Aflac ST0901 CHOANOME-Sirolimus in solid tumors (NCT01331135)[82]	Completed	Phase 1	Sirolimus	mTOR inhibitor	Apr 1, 2011
p28 in treating younger patients with recurrent or progressive central nervous system tumors (NCT01975116)	Completed	Phase 1	Azurin-derived cell-penetrating peptide p28	Peptide inhibitor of p53 ubiquitination	Nov 3, 2013
Simvastatin with topotecan and cyclophosphamide in relapsed and/or refractory pediatric solid and CNS tumors (AflacST1402) (NCT02390843)	Completed	Phase 1	Simvastatin	Hydroxy-methylglutaryl coenzyme A reductase inhibitor	Mar 18, 2015
A Phase 1 study of the EZH2 inhibitor tazemetostat in pediatric subjects with relapsed or refractory INI1-negative tumors or synovial sarcoma (NCT02601937)	Completed	Phase 1	Tazemetostat	EZH2 inhibitor	Nov 11, 2015
Ribociclib and everolimus in treating children with recurrent or refractory malignant brain tumors (NCT03387020)[83]	Completed	Phase 1	Ribociclib Everolimus	CDK4/6 inhibitor mTOR inhibitor	Jan 13, 2018

Abbreviations: CDK, cyclin dependent kinase; CNS, central nervous system; EZH2, enhancer of zeste homolog 2; mTOR, mechanistic target of rapamycin kinase; VEGF, vascular endothelial growth factor.

TABLE 3 Current open targeted therapy clinical trials involving patients with atypical teratoid/rhabdoid tumors

Title and trial ID	Phase	Target drug involved	Molecular mechanism	Starting date
Phase 2 study of alisertib therapy for rhabdoid tumors (NCT02114229)	Phase 2	Alisertib	Aurora A kinase inhibitor	May 14, 2014
Sirolimus in combination with metronomic chemotherapy in children with recurrent and/or refractory solid and CNS tumors (NCT02574728)	Phase 2	Sirolimus	mTOR inhibitor	Jun 1, 2015
Tazemetostat in treating patients with relapsed or refractory advanced solid tumors, non-Hodgkin lymphoma, or histiocytic disorders with *EZH2*, *SMARCB1*, or *SMARCA4* gene mutations (A Pediatric MATCH Treatment Trial) (NCT03213665)	Phase 2	Tazemetostat	EZH2 inhibitor	Jul 11, 2017
SJDAWN: St. Jude Children's Research Hospital Phase 1 study evaluating molecularly-driven doublet therapies for children and young adults with recurrent brain tumors (NCT03434262)	Phase 1	Ribociclib Sonidegib Trametinib	CDK4/6 inhibitor Hedgehog signaling inhibitor MEK inhibitor	Mar 5, 2018
A study of panobinostat in pediatric patients with solid tumors including MRT/ATRT (NCT04897880)	Phase 2	Panobinostat	Histone deacetylase inhibitor	Jan 9, 2019
Dose escalation study of CLR 131 in children, adolescents, and young adults with relapsed or refractory malignant tumors including but not limited to neuroblastoma, rhabdomyosarcoma, Ewings sarcoma, and osteosarcoma (NCT03478462)	Phase 1	CLR 131	Protein kinase B inhibitor	Apr 30, 2019
Study of nivolumab and ipilimumab in children and young adults with INI1-negative cancers (NCT04416568)	Phase 2	Nivolumab Ipilimumab	Anti-PD-1 Anti-CTLA-4	Aug 14, 2020
Tiragolumab and atezolizumab for the treatment of relapsed or refractory SMARCB1 or SMARCA4 deficient tumors (NCT05286801)	Phase 2	Atezolizumab Tiragolumab	Anti-PD-L1 Anti-TIGIT	Jun 16, 2022

Abbreviations: ATRT, atypical teratoid rhabdoid tumor; CDK, cyclin dependent kinase; CNS, central nervous system; EZH2, enhancer of zeste homolog 2; mTOR, mechanistic target of rapamycin kinase; MEK, mitogen-activated extracellular signal-regulated kinase; MRT, malignant rhabdoid tumor; PD-1, programmed cell death protein 1; CTLA-4, Cytotoxic T-lymphocyte associated protein 4; PD-L1, programmed death-ligand 1; TIGIT, T cell immunoreceptor with Ig and ITIM domains.

tazemetostat in children with AT/RTs and other INI1-negative tumors has been completed, although no results are yet available (NCT02601937).

Proteasome inhibitors

Proteasome inhibitors are capable of either directly inducing cancer cell death or sensitizing cancer cells to apoptosis. After high-throughput drug screening with 164 anticancer agents, Nakano et al.[59] found that the proteasome inhibitor bortezomib strongly inhibited AT/RT cell proliferation. Similarly, Thakur et al.[60] tested the cytotoxic effect of another proteasome inhibitor, carfilzomib, using a panel of pediatric solid tumor cell lines that included AT/RTs. Morin et al. [61] showed that marizomib strongly inhibited AT/RT cell growth both *in vitro* and *in vivo*; it has direct translational potential for patients with AT/RTs. Because the findings have been derived from sequencing analyses, the cytotoxic mechanisms that underlie the effects of proteasome inhibitors in AT/RT cells remain unclear.

Cell cycle regulation and associated signaling pathways

Cyclin D1 is a well-known cell cycle regulator that is reportedly overexpressed in AT/RT cell lines.[62,63] Although this overexpression was confirmed before the initial recruitment of AT/RT in a clinical trial of the CDK4/6 inhibitor ribociclib (NCT03387020), the link between cyclin D1 expression and SMARCB1 loss was revealed very recently. Xue et al.[64] demonstrated that cyclin D1 deficiency in AT/RTs is caused by SMARCB1 loss partly through the upregulation of *MIR17HG*, which produces mature miRNAs that target cyclin D1; they also found that this cyclin D1 deficiency in AT/RT cell lines results in considerable sensitivity to the CDK4/6 inhibitor palbociclib.

As mentioned in a previous section, tyrosine kinases are overexpressed in both AT/RT cell lines and primary tumor tissues; of these, the cell cycle-associated serine/threonine kinase aurora A is highly expressed.[65] Similar to HDAC inhibitors, aurora A inhibitors enhance radiosensitivity. The

aurora kinase inhibitor MLN8237 (alisertib) is currently in phase 1/2 clinical trials for various pediatric tumors; it has shown remarkable results. In one trial, four patients with relapsed or refractory AT/RTs were enrolled; all displayed disease stabilization with or without tumor regression.[66] Another clinical trial that combines alisertib with conventional therapy in newly diagnosed patients with RTs is in the recruitment stage (Table 3, NCT02114229).

Subtype-specific targeted therapy

Although exclusively subtype-specific drugs are not yet available, subtype susceptibilities to targeted therapy have been demonstrated. For example, platelet-derived growth factor receptor B was identified as a target in Group 2 cell lines (i.e., BT12, BT16, CHLA266, and CHLA06) in the work by Torchia et al.[33]; these cell lines all exhibited greater sensitivity to the platelet-derived growth factor receptor B inhibitors nilotinib and dasatinib than did Group 1 (ATRT-SHH) cell lines.[33] Transcriptome analyses have revealed other potential drug targets in AT/RTs that have not yet been tested in clinical trials. For example, fibroblast growth factor receptor 2 is specifically upregulated in ATRT-TYR, and AT/RTs are susceptible to treatment with fibroblast growth factor receptor inhibition, along with platelet-derived growth factor receptor inhibition.[67,68] Notably, Torchia et al.[33] reported that cell lines derived from ATRT-SHH tumors were highly sensitive to EZH2 inhibitors. In contrast to the findings in other embryonal tumors (e.g., medulloblastoma), aberrant expression patterns of SHH pathway members have not been found in ATRT-SHH. All changes in SHH pathway marker genes in ATRT-SHH are presumably directly or indirectly caused by the loss of SMARCB1.[69] Targeted drugs for SHH pathway inhibitors have diverse therapeutic indications and have demonstrated efficacy for medulloblastoma-SHH; such drugs should be investigated in the treatment of AT/RTs.[70] Tran et al.[71] reported that, compared with ATRT-SHH cell lines, ATRT-MYC cell lines were more sensitive to the proteasome inhibitor bortezomib. They also found that survival was prolonged in ATRT-MYC patient-derived xenograft mice that received bortezomib, suggesting that bortezomib may function as targeted therapy for ATRT-MYC. However, SMARCA4 has been shown to antagonize MYC activity.[72] Taken together, the results of laboratory studies highlight the potential applications of targeted therapies in each molecular subtype.

DISCUSSION

Advances in conventional chemotherapies and stratified treatment protocols have improved the 5-year OS of AT/RTs from 20% to nearly 50%. Nevertheless, most patients with AT/RTs are <3 years of age and have limited treatment options, as well as substantial toxic effects from current regimens. Thus, more effective and less harmful targeted therapies are needed.

Recent studies have shown the potential for treatment by controlling epigenetic dysregulation in AT/RTs. Clinical trials are ongoing for molecular targeted drugs that are designed to function either through the reactivation of enhancers that depend on SWI/SNF complexes or the inhibition of non-SWI/SNF-complex-dependent enhancers; a small amount of AT/RT patients are enrolled in such trials. The good news is that despite the enrollment of AT/RT patients in these trials being scarce, the targeted drugs involved have been designed increasingly specifically for tumorigenesis of AT/RTs over years. Comparing the earlier trials (Table 2) and the ongoing trials (Table 3), it is clear that molecular targets in clinical trials have shifted from usual carcinogenic pathways to AT/RTs-specific pathogenetic derangements.

However, most clinical trials of targeted drugs mentioned in this review are based on a larger sample database of patients with RTs or other embryonal CNS tumors; this status highlights the rarity and vulnerability of patients with AT/RTs. Firstly, because of the aggressive malignancy of AT/RTs, patients are barely able to complete the treatment process. Thus, it is difficult to distinguish treatment effects from the vulnerability of advanced patients. Second, because of the rarity of the disease, clinical trials usually lack control. This is another stumbling block to determine the treatment effect. Finally, the toxicity of targeted treatment, though milder than conventional therapies, may exaggerate in these children.

Novel diagnostic criteria indicate the presence of at least three molecular subtypes of AT/RTs: ATRT-TYR, ATRT-SHH, and ATRT-MYC—each has specific or overlapping targeting pathways. The ATRT-SMARCA4 subtype, for which there is no consensus, has great potential for advances in targeted therapeutic research. Notably, AT/RT stratification facilitates targeted drug selection, although it limits patient enrollment in clinical trials, thus prolonging an already time-consuming process. Gene therapy models and national or multicenter AT/RT registries may enable the management of these difficult situations.

Studies of the epigenetic dysregulation mechanism in AT/RT pathogenesis have substantially contributed to targeted therapies over the past decade. Based on the ongoing clinical trials, targeted drugs can provide insights regarding novel multimodal treatment protocols for intractable malignancies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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