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Advancing biology-based therapeutic approaches for atypical teratoid rhabdoid tumors

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Abstract

Atypical teratoid rhabdoid tumor (ATRT) is a rare, highly malignant central nervous system cancer arising in infants and younger children, historically considered to be homogeneous, monogenic, and incurable. Recent use of intensified therapies has modestly improved survival for ATRT; however, a majority of patients will still succumb to their disease. While ATRTs almost universally exhibit loss of *SMARCB1* (BAF47/INI1/SNF5), recent whole genome, transcriptome, and epigenomic analyses of large cohorts reveal previously underappreciated molecular heterogeneity. These discoveries provide novel insights into how *SMARCB1* loss drives oncogenesis and confer specific therapeutic vulnerabilities, raising exciting prospects for molecularly stratified treatment for patients with ATRT.

Rhabdoid tumors comprise a spectrum of poorly understood diseases that can arise in intracranial or extracranial locations, where they are respectively called atypical teratoid rhabdoid tumor (ATRT) or malignant rhabdoid tumor (MRT). ATRTs are central nervous system (CNS) tumors initially recognized based on morphologic resemblance to malignant renal rhabdoid tumors and subsequently defined as a distinct histogenetic entity in the late 1990s. Since 2000, ATRTs have been designated as a formal World Health Organization diagnostic category.[1] ATRTs are distinguished by biallelic loss of function mutations in SWItch/sucrose nonfermentable (SWI/SNF) related, matrix associated, actin dependent regulator of chromatin, subfamily B (*SMARCB1*), a tumor suppressor gene that encodes BAF47 (also called integrase interactor 1 [INI1], hSNF5), a core subunit of the SWI/SNF chromatin remodeling complex. A small percentage of ATRTs with wildtype *SMARCB1* harbor biallelic loss of *SMARCA4* that encodes SWI/SNF ATPase *Brahma*/SWI2-*related* gene 1 (BRG1).[2] ATRTs can exhibit substantial histopathologic variation and resemble other embryonal tumors; however, they are distinguished by negative immunostaining for INI1 or BRG1.[3,4] Given availability of INI1 and BRG1 immunohistochemistry in routine diagnostic neuropathology, ATRTs are now increasingly identified. ATRTs may arise in any CNS location, and the majority (70–80%) arise in children <3 years of age.[5] Up to one-third of children with ATRT have germline *SMARCB1* (or *SMARCA4*) alterations; these patients with rhabdoid tumor predisposition syndrome (RTPS) are at increased risk of developing multiple intra- and/or extracranial rhabdoid tumors at a very young age.[6] Although the true incidence of ATRTs is unknown, they are estimated to make up at least 20% of CNS tumors in children <3 years of age[7] and are the most common malignant CNS tumor of children age <1 year.[5]

Large-scale prospective treatment and demographic data on ATRTs are lacking; thus, studies of clinical prognosticators have been mainly derived from small retrospective cohorts. Metastatic disease, seen in 30–40% of ATRT patients at the time of diagnosis,[8–11] has been variably correlated with survival,[7–9,12–15] while supratentorial tumor location,[12,16] complete resection,[7,8,11,12] and response to chemotherapy and/or radiation therapy (RT)[11,12,15,17] has been associated with improved survival. Older age[9,12,17] has also been reported as a positive prognostic factor, though it is unclear whether this reflects a tendency to RT avoidance in younger children or distinct age-related tumor biology.[18,19]

ATRTs Exhibit Molecular Heterogeneity

Despite heterogeneity in location, treatment response, and disease stage in ATRT patients, whole exome and genome sequencing studies[18–22] indicate primary ATRTs have very low mutation rates with only recurrent *SMARCB1* alterations. This is in keeping with experimental studies that invoke epigenetic mechanisms as a major driver of cancers resulting from *SMARCB1* loss.[23] Collective studies from the Hospital for Sick Children (HSC) and German Cancer Research Center (DKFZ) showed that ATRTs comprise 3 main molecular subgroups with distinct epigenomic, transcriptional, clinicopathologic, and therapeutic features.[18,19] In a recent consensus publication by Ho et al., global methylation profiling of 388 primary ATRTs demonstrated that Group 1, 2A, and 2B ATRT subtypes reported by Torchia et al largely overlap, respectively, with the sonic hedgehog (SHH), tyrosine (TYR), and myelocytomatosis oncogene (MYC) subgroups reported by DKFZ.[24] These findings were further validated by transcriptional analysis of 172 primary ATRTs, including 21 with both methylation and transcription array data for which there was 96% subgroup concordance between platforms.

Although the consensus publication outlines enrichment of age categories and tumor location, there remains significant variation in clinical phenotypes within the 3 major ATRT subgroups. Infra- and supratentorial tumors, as well as metastatic disease, are found across ATRT subtypes. The HSC and DKFZ studies reported an enrichment of *SMARCB1* deletions in the MYC ATRT subgroup while Torchia et al also showed up to 20% of ATRTs exhibited other structural alterations and increased frequency of mutational events in the noncoding genome.[18] Of note, whole genome sequencing studies of MRTs, which by methylation exhibit similarity to the MYC subgroup, have revealed predominant intergenic mutational events[25] and frequent genomic rearrangements mediated by *PGDB5*,[25,26] an embryonic human transposase. How differences in mechanisms of *SMARCB1* loss, other genotypic events, and whether insertional mutagenesis events contribute to clinical heterogeneity within and across ATRT subgroups remains to be defined with deeper, comprehensive studies of larger cohorts.

Current Clinical Approaches to ATRTs

Currently, there is no standard treatment approach for ATRTs. Despite improved diagnostic recognition, there have been few ATRT prospective studies, and treatment data have largely been surmised from retrospective and small studies[5,7,27] (Table 1). ATRT therapy has generally followed evolution in approaches to infant brain tumors with use of conventional dose chemotherapy regimens in earlier studies and application of high dose chemotherapy (HDC) with stem cell rescue (SCR) in the more recent era as a mechanism of deferring or avoiding RT. Historical pan-infant brain tumor trials reported rapid progression and very poor outcomes for ATRT patients. In North American prospective trials CCG9921[28] and POG9233/34, most ATRT patients progressed within a year of diagnosis yielding progression-free survival (PFS) of <20%.[29] Similarly, patients treated with conventional chemotherapy with or without RT on the German HIT infant CNS tumor protocols had 3-year PFS and overall survival (OS) of only 13% ± 5% and 22% ± 6%, respectively.[12] The European Rhabdoid Registry (EU-RHAB)–based protocol demonstrated 6-year respective PFS/OS of 45% ± 9%/46% ± 10% for 31 patients treated using doxorubicin and ifosfamide-based chemotherapy as well as intraventricular and maintenance chemotherapy plus focal or craniospinal irradiation (CSI).[17] Though only short-term outcomes are reported,

Table 1 Summary of prospective trials and retrospective/registry studies of ATRTs

Protocol Name	Pts <3 years (n=)	HDC HDC/SCR	IT	Adjuvant RT Focal; WB; CSI (n)	Salvage RT Focal; WB; CSI (n)	PFS; OS (%)	Favorable Prognostic Factors	References
Prospective Clinical Trials								
POG9233/34 (N = 33)	33	–	–	–	–	5y: 0; 0	–	D. Strother (personal communication)
CCG9921 (N = 28)	28	–	–	1; 0; 1	9; 0; 0	5y: 14; 29	None significant	28
Head Start I (N = 7); Head Start II (N = 6)	9	CTE	–	–	2; 0; 2	3y: 23 ± 11; 23 ± 11	GTR	30
N/A (N = 8)	4	ETC	–		–	5y: 33; 50	–	31
IRS-III-like (N = 20)	12	–	Yes	11; 0; 4	–	2y: 53 ± 13; 70 ± 10	–	11
N/A (N = 9)	9	CTE, CM	No	0; 0; 1	1; 0; 4	3y: 0; 53 ± 17	–	32
Head Start III (N = 19)	19	CTE	–	–	5;0;0	3y: 21 ± 9; 26 ± 10	–	33
ACNS0333 (N = 65)	54	CT	No	40; 0; 6	–	4y: 37; 43	–	39
Retrospective Series								
COG 99703 (N = 8); IRS III-like (N = 7); CCG9921 (N = 6); Others (N = 21)	30	Yes (31%)	Yes (38%)	9; 0; 4	–	% Not reported	GTR; older age	7
SJMB96* (N = 7); BB98 (N = 7); PBTC-001 (N = 6); ICE (N = 1); Other (N = 9)	21	Yes (26%)	No	–	1; 0; 3	2y: 31 ± 9; 40 ± 10	RT	10
Various (N = 17)	2	No	Yes (12%)	0; 2; 15	–	% Not reported	Early RT	34
HIT 2000 (N = 18); HIT-SKK-92 (N = 9); HIT-SKK-91 (N = 6); Other (N = 17)	41	No	Yes (74%)	11; 0; 0	10; 0; 0	3y: 13 ± 5; 22 ± 6	Age > 1.2 years; Early complete response	12
AT/RT04 (N = 24); PNET-HR (N = 11); BB-SFOP (N = 9); Palliative (N = 9)		Yes (19%)	No	10; 0; 0	–	1y: 17%; 41%	Age > 2 years; M0 stage	9
IRS-III-like, baby brain, or ICE (N = 8); HDC/SCR (N = 23); Palliative (N = 10)	46	Yes (45%)	Yes (18%)	18; 0; 0	6; 0; 0	CC 2y OS: 27 ± 9; HDC/SCR 2y OS: 48 ± 12	HDC/SCR	8
Various (N = 31)	19	n/a	No	19; 0; 18	–	4y: 33 ± 10; 53 ± 10	Early RT	35
Rhabdoid 2007, EU-RHAB (N = 17)	14	Yes (65% at dx, 37% at relapse)	No	3; 0; 0	4; 0; 0	2y: 29 ± 11; 50 ± 12	–	36
IRS-III-like + HDC/SCR (N = 9)	5	CTE	Yes	5; 0; 0	–	5y: 89 ± 11; 100	–	14
Rhabdoid 2007 (N = 31)	23	Yes (23% at relapse)	Yes	21; 0; 2	–	6y: 45 ± 9; 46 ± 10	–	17
Various (N = 28)	12	Yes, n = 8	Yes, n = 3	8; 0; 20	–	% Not reported	Early RT; HDC/SCR	37

HDC/SCR: high-dose chemotherapy/stem cell rescue; RT: radiation therapy; IT: intrathecal or intraventricular; PF: posterior fossa; ST: supratentorial; CSI: craniospinal irradiation; tx: treatment; dx: diagnosis; alt: alternating with; HD MTX: high-dose methotrexate; CT: carboplatin, thiotepa; CECV: cisplatin, etoposide, cyclophosphamide, vincristine; CEIV: carboplatin, etoposide, ifosfamide, vincristine; CTE: carboplatin, thiotepa, etoposide; CM: cyclophosphamide, melphalan; IRS-III: 3rd Intergroup Rhabdomyosarcoma Study; VDC: vincristine, cyclophosphamide, doxorubicin; ICE: ifosfamide, carboplatin, etoposide; TI: trafosfamide, idarubicin; TE: trafosfamide, etoposide; NS: not statistically significant, or n/a: not applicable or not investigated. *Number of patients under 2 years of age instead of 3 years of age.
*Prospective series as footnote.

a prospective ATRT study by the Dana Farber Cancer Institute reported 2-year PFS/OS of 53% ± 13%/ 70 ± 10% in 20 evaluable patients using a regimen based on the *3rd* Intergroup *Rhabdomyosarcoma* Study (IRS-III) with triple intrathecal (IT) and focal RT or CSI.[11]

Similarly, improved survival for a proportion of ATRT patients was reported with HDC/SCR with the North American Head Start and CCG99703 trials representing the first generation of such studies. The Head Start II study reported improved outcome with high-dose methotrexate (HD-MTX)–based induction regimens[30]; however, the successor Head Start III study[31] reported inferior outcomes relative to contemporary studies[11,17,35,36] with frequent early progression and numerous toxic deaths. A Korean single institution HDC/SCR ATRT pilot study also reported frequent early progression with 3-year PFS/OS respectively of 0%/53% ± 17% and RT salvage needed for all survivors.[32,38] Similarly, an Italian study reported early progression in 6 of 8 patients treated with 4 induction cycles, HDC/SCR, and whole brain RT.[31] Interestingly, Slavc et al reported a provocative series with much improved 5-year PFS/OS of 89% ± 11%/100% in 9 patients treated with combined sarcoma-based induction with HDC/SCR, IT chemotherapy, and focal RT. Significantly, results of the Children's Oncology Group ACNS0333 trial, which represents the largest prospective ATRT study, has validated HDC/SCR as an important modality in ATRT. Using an HD-MTX induction, HDC/SCR consolidation, and age-adapted timing and field of RT, Reddy et al reported a 4-year event-free survival and OS of 37% and 43%, with few events occurring more than 2 years post diagnosis in 65 evaluable patients.[39]

Based on treatment of more common embryonal CNS tumors, such as medulloblastoma, RT has also been considered an important modality in ATRT therapy. However, use of RT in ATRT patients remains debated due to severe neurocognitive sequelae associated with whole brain RT in very young patients. As a consequence, a wide range of RT timing, dose, and volume has been used in retrospective ATRT studies.[8,12,27,40] There are currently no robust data to inform use of RT in this population. A Surveillance, Epidemiology, and End Results study concluded RT improved ATRT survival[13] based on examining receipt of RT and survival >6 months post diagnosis in 144 ATRT patients without accounting for impact of other treatment including chemotherapy and surgery. Similarly, a study of 31 ATRT patients treated with heterogeneous chemotherapy regimens suggested RT delays of ≥1 month post-surgery increased risk of disease recurrence.[35] However, the prospective ACNS0333 trial indicates timing of RT relative to chemotherapy did not impact survival.[39] Similarly, an Austrian study reported excellent outcomes in a series of 9 children treated with a HDC/SCR protocol and focal RT up to 9 months post-diagnosis.[14] Interestingly, the Canadian Pediatric Brain Tumor Consortium reported 2-year OS of 48% ± 12% in a retrospective cohort of 18 patients treated with HDC regimens, many of whom received no RT,[8] suggesting that a proportion of ATRT patients can be cured without radiation.

In aggregate, results of both prospective and retrospective studies utilizing conventional and HDC-based regimens indicate biological heterogeneity may underlie treatment-specific response and survival in ATRT patients.

ATRT Molecular Subgroups Have Varied Therapeutic Vulnerabilities

BAF47 is a core component of the polymorphic multisubunit SWI/SNF chromatin-remodeling complex which controls promoter and enhancer accessibility via nucleosome mobilization, a process normally antagonized by the polycomb repressive complexes (PRCs).[41,42] Loss of BAF47 has been shown to increase expression and activity of the PRC2 histone methyl transferase enhancer of zeste homolog 2 (EZH2)[43] and a spectrum of associated downstream oncogenic signaling pathways. Recent studies by Wang et al and Nakayama et al indicate BAF47 loss results in a residual SWI/SNF complex with impaired affinity for target promoters and distal enhancers in ATRT and MRT tumor cells.[41,44] These findings mirror studies in other SWI/SNF aberrant cancers lacking ARID1A or SMARCA4[45] and suggest that residual BAF47-deficient SWI/SNF complex may be important in maintaining oncogenic phenotypes in ATRTs and related tumors. Recent work by Erkek et al confirmed binding of residual SWI/SNF protein SMARCA4 at nearly all promoters in ATRT occupied by EZH2 but that lacked repressive H3K27me3 marks.[46] SMARCA4 knockdown led to increased H3K27me3 and decreased transcription at these specific sites, supporting the oncogenic potential of SMARCA4, as previously reported.[44,47] Together with recent functional epigenomic and modeling studies[18,19] defining unique lineage associated enhancer/super-enhancer profiles between ATRT subtypes, these findings suggest the nature of residual SWI/SNF complexes and associated lineage-related oncogenic pathways[48] (Fig. 1) may underlie specific therapeutic vulnerability observed in ATRTs subtypes.

Indeed, Torchia et al showed using gamma-secretase (DAPT*) and bone morphogenetic protein 2 (BMP)–pathway (dorsomorphin) inhibitors and gene knockdown experiments that ATRT cell lines subtyped as neurogenic Group 1 (SHH) and mesenchymal Group 2 (TYR/MYC) were distinctly dependent on Notch and BMP signaling which play respective roles in neurogenesis and mesenchymal differentiation.[18] They also showed multi–thymidine kinase 1 (TKI) (dasatinib, nilotinib) in vitro and in vivo inhibition of Group 2 (TYR/MYC) ATRT cells correlated with enhancer-mediated upregulation of platelet derived growth factor receptor B (PDGFRB), which has critical roles in mesenchymal differentiation. More recent subgroup classification of cell lines published by Ho et al defined cells susceptible to dasatinib and nilotinib (CHLA266/06, SH, BT16/12) as belonging to the MYC subgroup.[24] Thus, further work is required to elucidate the mechanism underlying this susceptibility.

In addition to differences in lineage-related vulnerabilities, Torchia et al also showed ATRT subtype specific cells had different sensitivities to 14 epigenetic

*N-[N-(3,5-difluorophenacetyl)-L-alanyl]-S-phenylglycine t-butyl ester.

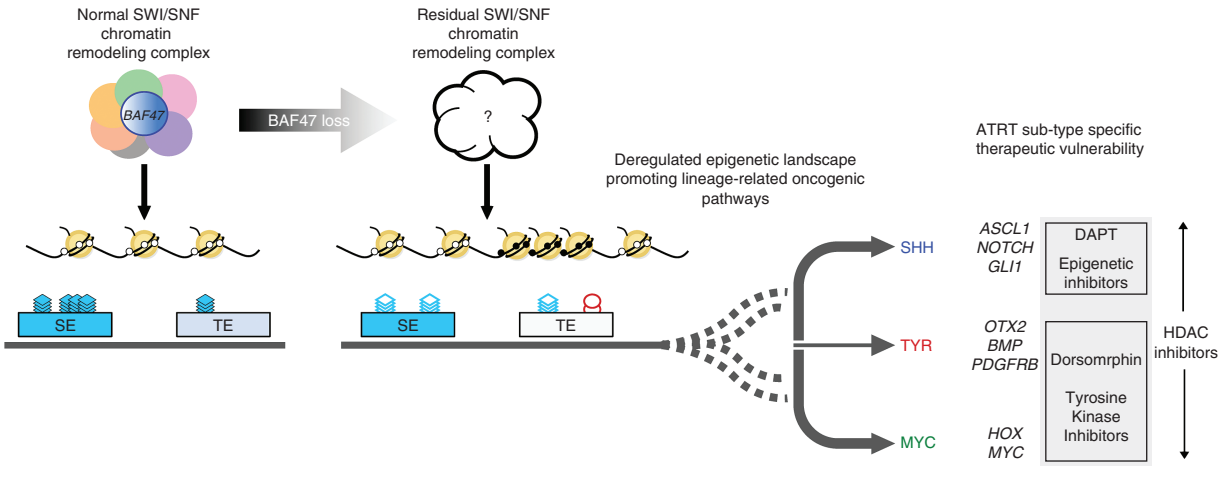

Fig. 1 Function of SWI/SNF chromatin remodeling complex with intact (left) and SMARCB1/BAF47 loss are schematized. Current evidence suggests SWI/SNF complexes mediate functions of typical and lineage associated super-enhancers (left). Loss of BAF47 which impairs SWI/SNF stability (right) is proposed to result in residual SWI/SNF complexes of various composition which mediate aberrant gene regulation at typical and super-enhancers to confer tumor subtype specific therapeutic vulnerabilities (dashed lines). ATRT subgroup specific enrichment patterns and reported vulnerabilities are shown. SE = super enhancer, TE = typical enhancer, blue stacks = H3K27ac marks, red circles = H3K27me3.

inhibitors including the **bromodomain** and extraterminal domain family (BET/bromodomain) protein, histone methyltransferases and histone deacetylases (HDACs). While HDAC inhibitors LAQ824 and J4 reduced growth of all ATRT cell lines, methyl transferase (UNC0638), EZH2 (UNC1999), and BET/bromodomain (JQ1) inhibitors had greater effects on growth of Group 1/SHH cell lines (CHLA02/04/05).[18] A better understanding of the nature of residual SWI/SNF complexes in ATRT molecular subgroups will be important for future development and understanding of how different epigenetic drugs may be tailored to ATRT molecular subtypes.

Although specific targetable activating mutations have not been reported in ATRTs, a number of promising targeted agents have been identified from in vitro and in vivo preclinical studies (Table 2), and some are currently in early phase clinical trials for patients with rhabdoid tumors, including cyclin-dependent kinase (CDK)4/6 inhibitors[49] (palbociclib [NCT03065062], abemaciclib [NCT02644460], ribociclib with everolimus [NCT03387020]), an aurora kinase inhibitor[50] (alisertib, NCT02114229), and an EZH2 inhibitor[50] (tazemetostat [NCT02601937 and NCT03213665]). Whether some or all of these agents will be pan-relevant or restricted to ATRT subtypes remains to be determined. Genomic studies suggest that MRTs may share molecular features with the MYC subclass of ATRTs.[24] Indeed, drug screening studies also indicate overlap in drug sensitivity in some ATRT and MRT cell lines.[51] The effect of HDAC inhibitor LAQ82 observed by Torchia et al in all ATRT cell lines is also notable, as low-dose panobinostat (LBH589, another HDAC inhibitor) has been shown to induce cellular senescence and promote differentiation in MRT cell lines.[52] Studies of transposase-mediated genomic rearrangements also suggest DNA damage pathways may represent common therapeutic vulnerabilities in MRTs and subclasses of ATRT.[26] Most recent studies by Leruste et al have demonstrated high CD8+T cell infiltration in TYR and MYC ATRTs. Using allografts derived from an inducible Smarcb1$^{flox/flox}$;Rosa26-Cre^{ERT2} ATRT model, they also demonstrated efficacy of immune checkpoint blockade indicating that immunotherapy may treat a proportion of ATRT subtypes.[51]

Future studies will need to examine how lineage-specific signaling inhibitors, multi-kinase or newer generations of PDGFRB inhibitors,[98] and other biologics can be combined with epigenetic inhibitors, immune-therapeutics, as well as conventional chemotherapy and/or RT to improve survival for ATRT patients.[49,82]

Refining Therapeutic Approaches to ATRTs

Some clinical factors that have most consistently been linked to poorer outcome in ATRT patients include young age, infratentorial location, germline *SMARCB1* mutations, and metastases. However, neither germline *SMARCB1* mutation nor metastases portended worse outcome in ACNS0333, the largest prospective trial. With the exception of spinal location (almost exclusively MYC subgroup), there is no consistent correlation of any other clinical prognostic factors with ATRT molecular subgroups, thus an integrated risk model may most precisely inform therapeutic approaches to ATRTs. Based on their initial small cohort study, Torchia et al proposed that neurogenic signatures indicated by high expression of achaete-scute homolog 1 and correlated with Group1/SHH ATRTs may represent a favorable prognostic factor and proposed a risk-stratification model for ATRTs which integrates clinical and molecular prognostic factors.[16] Notably, their data suggest that RT may be spared for a subset of patients with lower risk disease. As

Table 2 An overview of drugs, drug-like compounds, and chemical compounds tested on ATRT cell lines, animal models, and clinical trials*

Target/Mode of Action/Class		Phase of testing at which found to be effective or used		Refs
		Preclinical Studies	Early Phase Clinical Trials	
Classic Chemotherapy and DNA Damaging Agents	**Alkylating agents**	Carmustine,† thiotepa,† ifosfamide†	Carmustine, ifosfamide, temozolomide (nct00946335, nct01076530)	14,31, 54–59
	Antimetabolite		Intraventricular methotrexate (NCT01737671, NCT02684071)	60
	Guanosine analogs	Ribavarin†‡		61
	Intercalating agents	Actinomycin D,† idarubicin,† mitoxantrone,† doxorubicin†‡		51,54, 62
	Platinum compounds	Oxaliplatin†	Oxaliplatin (NCT00047177)	54,63, 64
	Topoisomerase inhibitors	Irinotecan,† etoposide†	Irinotecan (NCT00138216), Etoposide (NCT00392886)	62,65, 66
	Vinca alkaloid	Vinorelbine,† vincristine†‡		51,54
Kinase Inhibitors	**AKT**	MK-2206†		67
	ALK, TGFbeta	SB431542†		68
	Aurora A	Alisertib (MLN8237)†	Alisertib (NCT02114229)	69–72
	EGFR-HER2	**Lapatinib***†‡		73
	IGF-1R	NVP-AEW451†		67
	MEK	Selumetinib†		74
	mTOR	**Rapamycin***†	**Rapamycin*** (NCT03387020, NCT01331135)	54
	mTORC1/2	TAK228 (sapanisertib)†‡		75
	Multi-TKI	**Dasatinib,***†‡ imatinib,*† kw-2449,† **nilotinib***,† r-1530,*† **sorafenib,***† **sunitinib,***† **lenvatinib***†‡		18,51, 54,65, 72,76
	PDGFR/FGFR	Ponatinib*†		77
	PLK1	Volasertib (BI6727)*†‡		78
	PLK4	CFI-400945,†‡ CFI-400437,† centrinone,† centrinone-B†		72,79, 80
	PTK7	Vatalanib†		81
	VEGF	Axitinib,*† **cabozantinib,***†‡ **pazopanib,***†‡	Cediranib (NCT00326664)	4,72
Cell Cycle Targets	**CDK2 inhibitors**	Roscovitine†		54
	CDK4/6 inhibitors	**Palbociclib***†‡	**Ribociclib*** (NCT03387020), **Abemaciclib*** (NCT02644460)	49,82
Epigenetic Targeting Compounds	**Bromo/BET**	JQ1†‡		18,83, 84
	BRD9	BI-9564,† I-BRD9†		85
	Demethylating agent	**5-AZA-2′-deoxycytidine (decitabine)***†		62
	EZH2	3-Deazaneplanocin A (DZNep),† UNC1999,† **tazemetostat***†‡	**Tazemetostat*** (NCT02601937, NCT02875548, NCT02601950), Pediatric MATCH (NCT03213665)	18,62, 86,87
	G9a lysine methyltransferase	UNC0638†		18
	Histone deacetylase inhibitors (HDACi)	LAQ824 (Dacinostat),† **vorinostat (SAHA)**,*† **valproic acid,***† **SNDX-275 (entinostat)**,*† **trichostatin A***†	**Vorinostat*** (SAHA), (NCT01076530, NCT00217412), **valproic acid***	18,62, 88–92

Table 2 (continued)

Target/Mode of Action/Class		Phase of testing at which found to be effective or used		Refs
		Preclinical Studies	Early Phase Clinical Trials	
Pathway/Lineage Specific Compounds	**BMP**	Dorsomorphin*†		18
	Notch	DAPT*†	RO4929097 (NCT01088763)	18
	WNT inhibitor	Casin,*† niclosamide,† pyrvinium,† WNT-c59†		93
	Antibody		131-I-labeled monoclonal Ab: 8H9 (NCT00089245), 3F8 (NCT00445965)	
	Ornithine decarboxylase		DFMO (NCT03581240)	
	Oncolytic virus	Measles virus (MV)*†‡	Modified measles virus (MV-NIS, NCT02962167)	94
Other compounds	**ALDH inhibitor**	**Disulfiram***†‡		55
	LOX inhibitor	BAPN†‡		95
	Diferuoylmethane	Curcumin*†		54
	Flavonoid	**Apigenin***†		54
	PPARg agonist	Ciglitazone†		54
	Exosome release inhibitor	GW4869†		96
	MDM2, MDM4, MDMX	**Idasanutlin,***† ATSP-7041†	ALRN-6924 (NCT03654716)	97

*In vitro and in vivo studies are denoted with a dagger (†) or double dagger (‡), respectively. Agents without FDA approval are denoted with an asterisk (*). FDA approved targeted agents with preclinical or clinical data suggesting favorable blood–brain barrier penetration are bolded. Many of agents are FDA approved, and therefore with further preclinical testing (namely in vivo testing on transgenic mouse models and/or xenografts) may be promising agents to quickly translate into clinical use. Citations include only compounds deemed by the authors to be effective in their study.

much of their outcome data were collected over a period of change in treatment approaches from conventional chemotherapy to HDC regimens, the impact of ATRT subtypes on therapeutic outcomes needs to be validated in uniformly treated prospective cohorts. In contrast, Fruhwald et al recently reported biological subclassification of tumors from 84 patients who, while not treated on a prospective clinical trial, were treated more uniformly as per the EU-RHAB registry protocol and in multivariate analyses defined age <1 year and SHH or MYC subgroup designation as independently negative prognosticators of OS.[15] Such discrepancies highlight the need for international cooperation to collate prospective obtained clinical and biological data to develop an integrative model to stratify choice of chemotherapy and/or RT in addition to selecting appropriate subtyped tailored biologic agents.

Ultimately, it will be critical to incorporate rapid, reproducible, clinically certified molecular subgrouping tools, similar to those now implemented for medulloblastoma,[99] in future trials to fully evaluate the impact of disease biology on clinical outcomes. Global platforms such as RNASeq and DNA methylation arrays robustly demarcate molecular differences but may not be readily available in the clinical setting in most institutions. Hence, development of alternate, clinically certified, cost-effective methods, such as RNA-based NanoString and/or immunohistochemistry, is imperative for developing global clinical trials. Similarly, comparison and harmonization of preclinical reagents and models, and reevaluation of previously tested ATRT drugs in subtype-specific models will be important to inform future trial design. Validation of subtyping tools and studies of molecular subgroup correlation with clinical prognostic factors in a prospective clinical cohort will also be a critical next step. The recent establishment of a consensus on molecular grouping and nomenclature represents a first important step for advancing medical and scientific discussion and integration of molecular subgrouping into treatment planning for ATRTs.

Discovery of biological heterogeneity has tremendous potential to shape future risk and treatment stratification for patients with ATRT. However, the promise of biology-based therapies for patients with ATRT is tempered by the present lack of consensus regarding the best therapeutic backbone. Conflicting data surrounding treatment modalities, including HDC/SCR, RT, and IT chemotherapy, have yielded widely varied therapeutic practices, which has proven challenging for global collaborations for the next generation of ATRT trials. How chemotherapy backbone and/or tumor biology influences the requirement, timing, dose, and field of RT in ATRT therapy will be important to address in future prospective studies. Ultimately for this primarily infant disease, identification of patients for whom a combination of biologically targeted agents can delay, reduce, or completely abolish the need for intensive chemotherapy and RT is essential for not only advancing cure but also improving

quality of survival for these very young patients. Treatment modalities will have an impact on risk of second cancers[100] and will inform surveillance protocols for survivors with RTPS.[101] As long-term ATRT survivors have been a relatively recent phenomenon, neurocognitive outcomes for only a small number of ATRT patients[27] have been reported. Thus, measures of quality of life, neurocognitive, and functional outcomes of ATRT survivors will be important to incorporate in future clinical trials to evaluate the contribution of various treatment modalities to cognitive outcome in these very young survivors.

Summary

Currently, ATRT remains a highly lethal disease where maximum intensity chemoradiotherapeutic regimens have produced promising albeit modest gains in survival. The discovery of molecular heterogeneity in ATRTs has provided a much-needed advance. Together with integrated risk stratification, development of sensitive prognostic biomarkers and a wider spectrum of genetic therapeutic models will be needed to enable precise titration of treatment toxicity and efficacy for the very young ATRT population. Additionally, greater elucidation of the relevance of germline predisposition, a risk that should prompt genetic counseling for all children with ATRT, and genotype-phenotype correlations in those with RTPS will be important.

The field and interest in clinical and basic science studies of ATRT have grown substantially for this once neglected orphan disease. This has been underscored by the scope of a 2018 international ATRT meeting which also enabled harmonization of nomenclature and cross-fertilized clinical and scientific interest in this disease and bodes well for the future of ATRT patients.

Keywords

ATRT | enhancer | epigenomics | rhabdoid tumors | subgroup-specific therapeutics

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