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CORRESPONDENCE

DNA-methylation subgroups carry no prognostic significance in ATRT-SHH patients in clinical trial cohorts

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Atypical teratoid/rhabdoid tumors (ATRT) are malignant embryonal tumors, most often presenting in children under three years of age [7]. Three consensus ATRT molecular subtypes have been established, designated ATRT-SHH, ATRT-MYC, and ATRT-TYR [4, 5]. The ATRT-TYR group has been associated with better overall survival [3, 10]; whereas, patients with ATRT-SHH have inferior outcomes, largely attributable to an increased risk of metastasis [10]. Recently, Federico et al. analyzed a registry cohort of ATRT-SHH and reported three molecular subgroups designated ATRT-SHH 1A, 1B, and 2 [2]. While some novel molecular classes may represent important determinants of clinical outcome or surrogates of alternative driver mutations [6], others may reflect biologically driven differences, but lack clear clinical import. To validate the three ATRT-SHH molecular subgroups and add insight into the clinical significance of these molecular classes, we evaluated the clinical features and outcome data for ATRT-SHH patients treated in St. Jude Children's Research Hospital (SJCRH) initiated multi-institutional clinical trials ($n=39$): SJYC07, SJMB03, SJATRT, or in a consortium trial open at St. Jude: PBTC-001 ($n=2$). Patients equivalently treated on non-protocol treatment plan (NPTP) ($n=2$) at St. Jude were also included where available.

First, we validated three subgroups of ATRT-SHH using publicly available datasets containing ATRT-SHH tumors [1, 3, 4] (Supplemental Methods and Fig. S1). Next, we assigned consensus labels to SJCRH cases using a combination of unsupervised and semi-supervised methods [8–10] (Fig. S2). Consensus subgroup labels were reliably assigned to 41/43 cases, with 14 designated ATRT-SHH-1A, 11 ATRT-SHH-1B, and 16 ATRT-SHH-2 (Table S1). Analysis of the clinical data from these 41 patients supported the previous observations of subgroup-specific differences in tumor site ($p=0.005$) [2]. We observed an enrichment of ATRT-SHH-2 in the infratentorial compartment and ATRT-SHH-1 in the supratentorial compartment (Table S1). We also confirmed the previously observed difference in age at diagnosis with the ATRT-SHH-1B patients presenting at a median age of 3.5 years, compared to 1.1 years for both ATRT-SHH-1A and ATRT-SHH-2 ($p=0.008$). No differences were identified with respect to gender or germline cancer predisposition among subgroups (Table S1).

Next, we evaluated the patient outcomes for the thirty-six patients who enrolled on frontline trials or received NPTP equivalent to frontline protocols at diagnosis, including SJYC07 ($n=27$), SJMB03 ($n=5$), and PBTC-001 ($n=4$). In contrast to the findings reported by Federico and colleagues [2], we did not observe differences in survival, including overall survival (OS) or progression-free survival (PFS) (Fig. 1a, b). We also evaluated ATRT-SHH subgroups for survival differences after considering metastatic status at presentation or with respect to post-recurrence survival but found no significant difference (data no shown).

In summary, our findings validated reported substructure within the ATRT-SHH molecular group and confirmed

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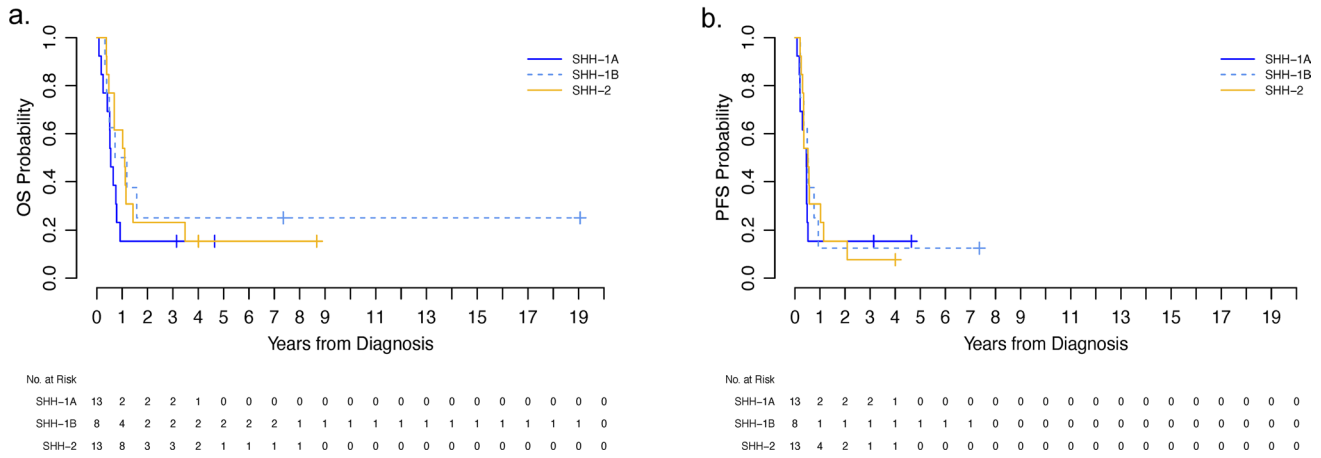

Fig. 1 Kaplan–Meier survival curves for combined frontline trial patients. Five-year OS (**a**), PFS (**b**) by ATRT-SHH molecular subgroup

the primary reported clinical correlates of enrichment for infratentorial location in the ATRT-SHH-2 subgroup and an older age of presentation in the ATRT-SHH-1B subgroup [2]. However, we found no significant difference in patient survival among subgroups in frontline clinical trials. There are several possible explanations for the differences observed between our cohort and the previously published cohort. First, our cohort contains significantly fewer patients and, therefore, may be underpowered to detect group-specific survival signal. Additionally, differences in therapeutic interventions could be masking subgroup-specific outcome differences. The ATRT-SHH-1B patients previous report had a significantly older median age compared to our cohort (8.9 years old compared to 3.5 years, respectively), increasing the proportion of cases eligible for craniospinal irradiation (CSI). We previously reported that ATRT patients receiving upfront CSI show significantly better survival compared to patients receiving focal postoperative radiation alone [10]. Although we find no support in our cohorts that the ATRT-SHH subgroups should be used as the basis for trial stratification or clinical decision-making, it will be important to monitor for clinical impact in subsequent studies.

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Data availability The data that support the findings of this study are available from the corresponding author (B.A.O) upon reasonable request.

Declarations

Conflict of interest The authors declare no potential conflicts of interest.

References

1. Capper D, Jones DTW, Sill M, Hovestadt V, Schrimpf D, Sturm D et al (2018) DNA methylation-based classification of central nervous system tumours. Nature 555:469–474. https://doi.org/10.1038/nature26000
2. Federico A, Thomas C, Miskiewicz K, Woltering N, Zin F, Nemes K et al (2022) ATRT-SHH comprises three molecular subgroups with characteristic clinical and histopathological features and prognostic significance. Acta Neuropathol 143:697–711. https://doi.org/10.1007/s00401-022-02424-5
3. Fruhwald MC, Hasselblatt M, Nemes K, Bens S, Steinbugl M, Johann PD et al (2020) Age and DNA methylation subgroup as potential independent risk factors for treatment stratification in children with atypical teratoid/rhabdoid tumors. Neuro Oncol 22:1006–1017. https://doi.org/10.1093/neuonc/noz244
4. Ho B, Johann PD, Grabovska Y, De Dieu Andrianteranagna MJ, Yao F, Fruhwald M et al (2020) Molecular subgrouping of atypical teratoid/rhabdoid tumors-a reinvestigation and current consensus. Neuro Oncol 22:613–624. https://doi.org/10.1093/neuonc/noz235

5. Johann PD, Erkek S, Zapatka M, Kerl K, Buchhalter I, Hovestadt V et al (2016) Atypical teratoid/rhabdoid tumors are comprised of three epigenetic subgroups with distinct enhancer landscapes. Cancer Cell 29:379–393. https://doi.org/10.1016/j.ccell.2016.02.001
6. Kumar R, Liu APY, Orr BA, Northcott PA, Robinson GW (2018) Advances in the classification of pediatric brain tumors through DNA methylation profiling: from research tool to frontline diagnostic. Cancer 124:4168–4180. https://doi.org/10.1002/cncr.31583
7. Ostrom QT, Patil N, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS (2020) CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2013–2017. Neuro Oncol 22:iv1–iv96. https://doi.org/10.1093/neuonc/noaa200
8. Tran QT, Alom MZ, Orr BA (2022) Comprehensive study of semi-supervised learning for DNA methylation-based supervised classification of central nervous system tumors. BMC Bioinformatics 23:223. https://doi.org/10.1186/s12859-022-04764-1
9. Upadhyaya SA, Campagne O, Billups CA, Orr BA, Onar-Thomas A, Tatevossian RG et al (2022) Phase II study of alisertib as a single agent for treating recurrent or progressive atypical teratoid/rhabdoid tumor. Neuro Oncol. https://doi.org/10.1093/neuonc/noac151
10. Upadhyaya SA, Robinson GW, Onar-Thomas A, Orr BA, Johann P, Wu G et al (2021) Relevance of molecular groups in children with newly diagnosed atypical teratoid rhabdoid tumor: results from prospective St. Jude multi-institutional trials. Clin Cancer Res 27:2879–2889. https://doi.org/10.1158/1078-0432.CCR-20-4731