Towards risk-adapted therapy for rhabdoid tumour subgroups

Atypical teratoid rhabdoid tumour is an aggressive paediatric embryonal brain tumour with a poor prognosis despite intensive multimodal therapy. Children older than 3 years with complete tumour resection and early irradiation might have better chances of survival.1 The characteristics of atypical teratoid rhabdoid tumours are a biallelic inactivation of SMARCB1 (hSNF5/INI1/BAF47), a core subunit of the highly-conserved SWI/SNF chromatin-remodelling complexes that have different roles in transcriptional and epigenetic regulation of cell signalling, growth, and differentiation.2 First recognised in malignant teratoid rhabdoid tumours are a biallelic inactivation of SMARCB1 mutation, the only recurrent genetic alteration in atypical teratoid rhabdoid tumours. Gene expression and clinicopathological analysis of childhood atypical teratoid rhabdoid tumours showed that robust ASCL1 antibody immunostaining reliably differentiated the two molecular groups. In a univariate analysis of 70 patients who received treatment with curative intent, the investigators reported that ASCL1 expression was prognostic of better 5-year overall survival than was no expression (35% [95% CI 13–57] vs 20% [6–34], p=0·033). Interestingly, among patients treated with chemotherapy alone, group 1 patients had significantly better 5-year overall survival (34% [7–61]) than did group 2 patients (9% [0–21]; p=0·001), implying greater intrinsic chemosensitivity in group 1 patients, justifying a radiation-sparing approach in young patients in this group to avoid neurocognitive sequelae, without compromising survival. Extent of resection was significantly greater in group 1 patients irrespective of location, indicating enrichment of cell adhesion and migration genes in group 2 tumours that might promote a more infiltrative or metastatic tumour phenotype.

Integrating molecular and clinicopathological analyses, the investigators proposed three separate risk categories of atypical teratoid rhabdoid tumours: the average risk group comprised older children with completely resected, supratentorial atypical teratoid rhabdoid tumours, high ASCL1 expression with a significantly better 5-year overall survival of 60% (95% CI 17–100) than in the other categories; very high risk comprised younger children with incompletely resected or metastatic infratentorial, ASCL1-negative atypical teratoid rhabdoid tumours with a dismal 5-year overall survival of 6% (0–16) and rapid disease progression; and high risk comprised children with a 5-year overall survival of 32% (95% CI 14–50), which included patients with all other features. Importantly, average-risk patients treated with chemotherapy alone had the best outcomes, whereas highest-risk patients had a dismal prognosis irrespective of therapy.

This study has several limitations. In both the discovery and validation cohorts, full clinical and
treatment data were unavailable for many patients. This multinational cohort spanned decades and diverse treatment approaches. Only univariate analyses adjusted for ASCL1 status were used to assess the prognostic significance of molecular subtyping because the cohort was underpowered for multivariate analyses. In risk-stratified analyses, the average-risk cohort was small (n=6). Prospective validation of the proposed risk-stratification in current protocols for atypical teratoid rhabdoid tumours is crucial to confirm these results and refine group-specific diagnostic molecular markers.

Nevertheless, this important study marks the first step towards an integrated, risk-adapted, therapeutic approach for atypical teratoid rhabdoid tumours: avoiding radiation in younger, average-risk patients and integrating novel therapies early for very high-risk patients. Inhibitors of NOTCH, BMP, and LIN28/RAS/MAP kinase signalling are candidates with promising preclinical efficacy in models of atypical teratoid rhabdoid tumours. The MEK inhibitor selumetinib, Aurora kinase, and EZH2 inhibitors have also shown encouraging specific preclinical activity against atypical teratoid rhabdoid tumours, leading to current or planned paediatric trials. Indeed, efficacy has been reported with the Aurora kinase A inhibitor alisertib in children with atypical teratoid rhabdoid tumours. Rapid validation of these results might herald a promising new therapeutic era of risk-adapted trials incorporating novel agents for this group of children.

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We declare no competing interests.