ABSTRACT

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Clinical phenotypes and prognostic features of embryonal tumours with multi-layered rosettes: a Rare Brain Tumor Registry study.

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BACKGROUND: Embryonal tumours with multi-layered rosettes (ETMRs) are a newly recognised, rare paediatric brain tumour with alterations of the C19MC microRNA locus. Due to varied diagnostic practices and scarce clinical data, disease features and determinants of outcomes for these tumours are poorly defined. We did an integrated clinicopathological and molecular analysis of primary ETMRs to define clinical phenotypes, and to identify prognostic factors of survival and key treatment modalities for this orphan disease.

METHODS: Paediatric patients with primary ETMRs and tissue available for analyses were identified from the Rare Brain Tumor Consortium global registry. The institutional histopathological diagnoses were centrally re-reviewed as per the current WHO CNS tumour guidelines, using histopathological and molecular assays. Only patients with complete clinical, treatment, and survival data on Nov 30, 2019, were included in clinicopathological analyses. Among patients who received primary multi-modal curative regimens, event-free survival and overall survival were determined using Cox proportional hazard and log-rank analyses. Univariate and multivariable Cox proportional hazard regression was used to estimate hazard ratios (HRs) with 95% CIs for clinical, molecular, or treatment-related prognostic factors.

FINDINGS: 159 patients had a confirmed molecular diagnosis of primary ETMRs (median age at diagnosis 26 months, IQR 18-36) and were included in our clinicopathological analysis. ETMRs were predominantly non-metastatic (94 [73%] of 128 patients), arising from multiple sites; 84 (55%) of 154 were cerebral tumours and 70 (45%) of 154 arose at sites characteristic of other brain tumours. Hallmark C19MC alterations were seen in 144 (91%) of 159 patients; 15 (9%) were ETMR not otherwise specified. In patients treated with curative intent, event-free survival was 57% (95% CI 47-68) at 6 months and 31% (21-42) at 2 years; overall survival was 29% (20-38) at 2 years and 27% (18-37) at 4 years. Overall survival was associated with non-metastatic disease (HR 0·48, 95% CI 0·28-0·80; p=0·0057) and non-brainstem location (0·42 [0·22-0·81]; p=0·013) on univariate analysis, as well as with gross total resection (0·30, 0·16-0·58; p=0·0014), high-dose chemotherapy (0·35, 0·19-0·67; p=0·0020), and radiotherapy (0·21, 0·10-0·41; p<0·0001) on multivariable analysis. 2-year event-free and overall survival was 0% at 2 years in patients treated with conventional chemotherapy without radiotherapy (regardless of surgery extent), and 21% (95% CI 1-41) and 30% (6-54), respectively, in patients treated with high-dose chemotherapy, and gross total resection without radiotherapy. 2-year event-free survival in patients treated with high-dose chemotherapy and radiotherapy was 66% (95% CI 39-93) for patients with gross total resection and 44% (7-81) for patients with sub-total resection. 2-5-year overall survival was 66% (95% CI 33-99, p=0·038) for patients with gross total resection and 67% (36-98, p=0·0020) for patients with sub-total resection.

INTERPRETATION: Prompt molecular diagnosis and post-surgical treatment with intensive multi-modal therapy tailored to patient-specific risk features could

improve ETMR survival.

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