ABSTRACT

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Molecular classification and outcome of children with rare CNS embryonal tumors: results from St. Jude Children's Research Hospital including the multi-center SJYC07 and SJMB03 clinical trials.

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Methylation profiling has radically transformed our understanding of tumors previously called central nervous system primitive neuro-ectodermal tumors (CNS-PNET). While this marks a momentous step toward defining key differences, reclassification has thrown treatment into disarray. To shed light on response to therapy and guide clinical decision-making, we report outcomes and molecular features of children with CNS-PNETs from two multi-center risk-adapted studies (SJMB03 for patients ≥ 3 years; SJYC07 for patients < 3 years) complemented by a non-protocol institutional cohort. Seventy patients who had a histological diagnosis of CNS-PNET or CNS embryonal tumor from one of the new categories that has supplanted CNS-PNET were included. This cohort was molecularly characterized by DNA methylation profiling (n = 70), whole-exome sequencing (n = 53), RNA sequencing (n = 20), and germline sequencing (n = 28). Clinical characteristics were detailed, and treatment was divided into craniospinal irradiation (CSI)-containing (SJMB03 and SJMB03-like) and CSI-sparing therapy (SJYC07 and SJYC07-like). When the cohort was analyzed in its entirety, no differences were observed in the 5-year survival rates even when CSI-containing therapy was compared to CSI-sparing therapy. However, when analyzed by DNA methylation molecular grouping, significant survival differences were observed, and treatment particulars provided suggestions of therapeutic response. Patients with CNS neuroblastoma with FOXR2 activation (CNS-NB-FOXR2) had a 5-year event-free survival (EFS)/overall survival (OS) of 66.7% ± 19.2%/83.3% ± 15.2%, and CIC rearranged sarcoma (CNS-SARC-CIC) had a 5-year EFS/OS both of 57.1% ± 18.7% with most receiving regimens that contained radiation (focal or CSI) and multidrug chemotherapy. Patients with high-grade neuroepithelial tumor with BCOR alteration (HGNET-BCOR) had abysmal responses to upfront chemotherapy-only regimens (5-year EFS = 0%), but survival extended with salvage radiation after progression [5-year OS = 53.6% ± 20.1%]. Patients with embryonal tumor with multilayered rosettes (ETMR) or high-grade glioma/glioblastoma multiforme (HGG/GBM) did not respond favorably to any modality (5-year EFS/OS = 10.7 ± 5.8%/17.9 ± 7.2%, and 10% ± 9.0%/10% ± 9.0%, respectively). As an accompaniment, we have assembled this data onto an interactive website to allow users to probe and query the cases. By reporting on a carefully matched clinical and molecular cohort, we provide the needed insight for future clinical management.

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