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The challenges in treating embryonal tumors with multilayered rosettes (ETMR) and other infant brain tumors

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Infant brain cancers encompass a heterogenous group of tumors with distinct genetic drivers and are associated with significant therapeutic challenges and poor overall survival (Figure 1). Embryonal tumors with multilayered rosettes (ETMR), characterized by amplification of the chromosome 19 miRNA cluster (C19MC), represent a particularly aggressive infant brain tumor with a dismal prognosis. In this issue of Neuro-Oncology, Juhnke et al report the outcomes of the largest cohort of children diagnosed with ETMR.[1] Their results confirm tumor location, extent of resection, and the presence of metastasis as independent prognostic factors, with superior outcomes in children with completely resected, non-metastatic, and supratentorial disease. Importantly, the authors demonstrate the significant improvement in overall survival for patients with supratentorial disease employing intensified high-dose multi-agent chemotherapy approaches compared to those treated with other approaches.

ETMRs were first identified to be a specific disease entity in the early 2000s[2,3] and epitomize the challenges faced when treating infants with malignant brain tumors. The current study highlights the importance of treatment strategies that optimize local control while preventing and/or treating disseminated disease. One of the most effective anti-tumor modalities of treatment, radiation therapy, is prohibitive for infants and young children. While craniospinal irradiation is often used to control or prevent metastatic disease in older children, similar treatment in the youngest of children results in devastating effects on neurocognition and growth. Thus, alternate anti-tumor approaches to target the entire craniospinal axis are leveraged, frequently including intensified and high-dose multi-agent chemotherapy as described by Juhnke et al. Indeed, similar approaches have also been shown to improve outcomes in other infant diseases, including medulloblastoma[4,5] and atypical teratoid rhabdoid tumors (ATRT).[6,7] Yet, intensive chemotherapy regimens are also associated with dose-limiting toxicities. Direct injection of chemotherapy into the intrathecal space through an in-dwelling ventricular catheter represents an alternate approach for the prevention and/or treatment of leptomeningeal spread of disease. The use of intrathecal administration of agents such as methotrexate, cytarabine, etoposide, and topotecan has been explored, however, the relative efficacies of each of these drugs have not been systematically evaluated.

Unique cancers like ETMR, ATRT, and gliomas harboring somatic gene alterations in neurotrophic tyrosine receptor kinase (NTRK), MET proto-oncogene (MET), ROS1, or anaplastic lymphoma kinase (ALK),[8,9] ependymomas, medulloblastoma, pineoblastomas, and choroid plexus tumors, represent the majority of infant tumors. Each of these entities is extremely rare, representing the challenge of accrual of sufficient numbers of patients to evaluate specific treatment approaches in the context of clinical trials. To overcome this challenge, Juhnke et al retrospectively identified patients with molecularly defined ETMR that were treated in the context of either the P-HIT clinical trial or HIT2000-interim-registry, allowing them to combine the clinical features of 35 ETMR patients treated on these protocols. Multi-institutional and international collaboration through consortia have proven essential to the ability to perform clinical trials to prospectively assess efficacy of treatment approaches in these rare populations.

Recent landmark genomic profiling efforts have revealed multiple somatic drivers of infant brain tumors,[8,9] creating optimism for precision medicine approaches. As an example, small molecule inhibitors targeting NTRK and ALK have been developed and have received FDA approval for the treatment of pediatric solid tumors with NTRK rearrangements. However, strategies to target other alterations, including the C19MC amplicon that define ETMRs, remain elusive. While significant efforts are underway across laboratories to identify novel therapeutic approaches for these unique tumors, optimal strategies to incorporate and assess these new agents rapidly in clinical trials remain challenging.

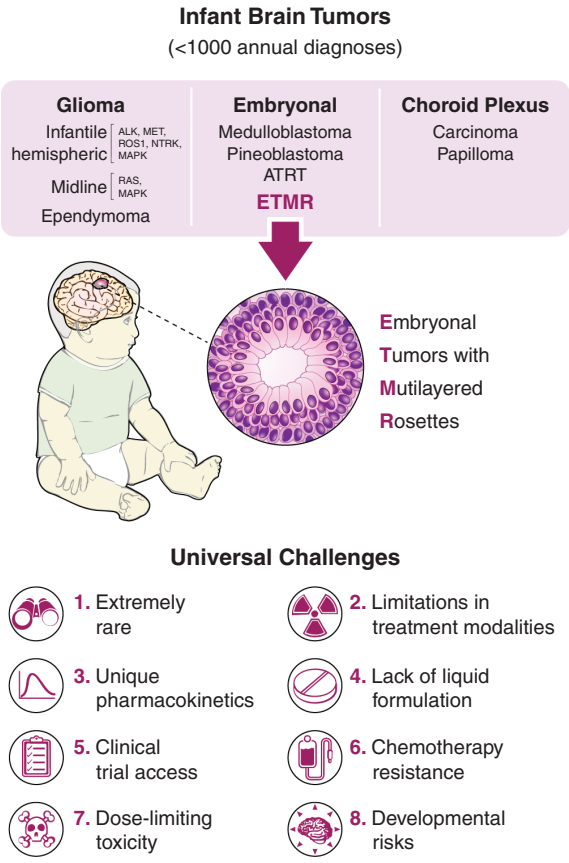

Fig. 1 Infant brain tumors are rare (<1000 total annual diagnoses/year which varies by subtype) and encompass a heterogeneous group of tumors, including embryonal tumors with multilayered rosettes (ETMR). Their treatment is associated with a number of treatment challenges that are shown.

Conducting clinical trials including infants also requires specific considerations. First, drug formulations are often restrictive in their use in children who are unable to swallow intact tablets or capsules. Determining release and absorption of crushed tablets, or developing powder or liquid formulations, keeping in mind potential enteral tube dependency, may help overcome this barrier. Second, drug metabolism is unique in infants and often results in clinical trial eligibility to restrict enrollment to children who are at least 1 year of age. Dose-finding and toxicity-defining phase 1 trials should thus include infants, allowing pharmacokinetic assessment of each compound in this age group. Third, trials should include assessments of longer-term growth and development to allow for the identification of the late effects of treatment. Moreover, it is important to anticipate potential side effects of all new targeted inhibitors on normal developmental programs in vital organs while tracking associated long-term toxicity.

Finally, while the majority of childhood cancers arise sporadically, recent studies have implicated germline alterations in 5%-15% of children.[10] This is particularly important as a diagnosis of cancer in the early years of life may signal the presence of a familial cancer predisposition syndrome. For example, choroid plexus carcinomas are often associated with a diagnosis of Li-Fraumeni Syndrome; ATRT is associated with a rhabdoid tumor predisposition. Clinical germline sequencing, coupled with genetic counseling, should be included in the care of all infants, if not all children, diagnosed with brain tumors.

Brain tumors are difficult to cure across all age groups. The additional obstacles in treating infants due to the size and locations from which tumors arise, the surgical risks of such large complex operations, the considerations of therapy administration as well as the potential devastating morbidities from the many treatment approaches, all contribute to the need for specialized multidisciplinary teams experienced in treating infants with brain tumors in order to optimize their safe and meaningful survival.

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