Medulloblastoma: From Myth to Molecular.

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Abstract

Current therapies for medulloblastoma were introduced primarily in the 1980s and consist of predominantly cytotoxic, nontargeted approaches. Mortality from medulloblastoma remains significant. In addition, many survivors suffer from severe treatment-related effects of radiation and cytotoxic chemotherapy. Further intensification of nonspecific therapy is unlikely to offer additional benefits, because survival rates have reached a plateau. Recent publications in medulloblastoma have revolved largely around the recognition that medulloblastoma per se does not exist, but rather, that there are a group of histologically similar but clinically and molecularly distinct entities that have been grouped under that rubric. Distinguishing the four molecular subgroups of medulloblastoma-wingless (WNT), sonic hedgehog (SHH), group 3, and group 4-in the daily treatment of patients, as well in the setting of clinical trials, is an important challenge in the near term for the pediatric neuro-oncology community. The preponderance of morbidity in treating patients with medulloblastoma is secondary to the treatment or prophylaxis of leptomeningeal metastases, and the cause of most deaths is leptomeningeal metastases. Recurrence of medulloblastoma is a nearly universally fatal event, with no significant salvage rate. The extent of spatial and temporal intratumoral heterogeneity as medulloblastoma metastasizes to leptomeninges and as it evolves in the face of radiation and cytotoxic chemotherapy is just beginning to be understood as a major barrier to therapeutic success. Pediatric neuro-oncology clinicians and scientists must now determine how best to incorporate rapid changes in our biologic understanding of medulloblastoma into the next generation of upfront clinical trials, with the goal of both improving survival for the highest-risk patients and improving quality of life for survivors.