Diffuse intrinsic pontine glioma: pathophysiological and clinical aspects of a pediatric brain tumor resistant to current therapies

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Diffuse intrinsic brainstem gliomas constitute 15-20% of all CNS tumors in children, and are the main cause of death in children with brain tumors. The MRI characteristics of diffuse intrinsic brain stem gliomas include diffuse infiltrative enlargement of the pons and/or rostral medulla. T1 MRI sequences usually show mass effect and reduced signal compared with normal brain. T2 MRI sequences often reveal high-signal regions of tumor infiltration with rostral extension into the midbrain and brachium pontis and lateral extension into the cerebellar peduncles. The 4th ventricle is usually distorted; however, obstructive hydrocephalus is distinctly uncommon at initial presentation.

Early in the clinical course, tumor cells infiltrate widely throughout brainstem structures but still permit neurological function to remain at normal or near-normal levels. Consequently, removal of tumor is likely to result in severe neurological deficits. Diffuse brain stem gliomas are among the least responsive and most resistant childhood solid tumors. Conventional treatment consists of 55 Gy involved-field radiation therapy administered in single daily fractions of approximately 1.8-2 Gy. This approach results in median survival of 9-13 months from diagnosis. Despite encouraging single institution reports suggesting prolonged progression-free survival for children treated with hyperfractionnated radiation therapy in which total radiation doses reached 78 Gy, larger cooperative trials failed to demonstrate a significant advantage for hyperfractionnated radiation. Results from chemotherapy trials have been similarly disappointing. Even when the most aggressive chemotherapy approaches are used, such as high-dose chemotherapy followed by peripheral blood stem cell reinfusion, results are usually limited to relatively brief duration responses and few instances of significant tumor reduction lasting 12 months or longer. Accordingly, the identification of novel therapeutic strategies remains a major goal.

Recent advances in stem cell biology, cell signalling, genome and computational science and genetic model systems have revolutionized our understanding of the mechanisms underlying the genetics and biology of malignant glioma in adult patients. To progress, malignant gliomas stimulate the formation of new blood vessels through processes driven primarily by vascular endothelial growth factor (VEGF). However, the resulting vessels are structurally and functionally abnormal, and contribute to a hostile microenvironment (low oxygen tension and high interstitial fluid pressure) that selects for a more malignant phenotype. Emerging preclinical and clinical data indicate that anti-VEGF therapies are potentially effective in malignant glioma and can transiently normalize tumor vessels. Several low molecular weight signal transduction inhibitors have been examined in preclinical and clinical malignant glioma trials. The efficacy of these agents as monotherapies has been modest, at best; however, small subsets of patients who harbor specific genetic changes in their tumors may display favorable clinical responses to defined small molecule inhibitors. Multitargeted kinase inhibitors or combinations of agents targeting different mitogenic pathways may overcome the resistance of tumors to single-agent targeted therapies. Well designed studies of small molecule inhibitors will include assessment of safety, drug delivery, target inhibition and correlative biomarkers to define mechanisms of response or resistance to these agents. Predictive biomarkers will enrich for patients most likely to respond in future clinical trials. Additional clinical studies will combine novel targeted therapies with radiation, chemotherapies and immunotherapies.