

Of Mice and Men – Exploring the Challenges to and Progression in the Treatment of Diffuse Intrinsic Pontine Gliomas

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Chemo-resistant and incurable, DIPG accounts for 10-20% of all paediatric brain tumours. Comprising appx. 50% of pons, they often present with a clinical triad of long-tract signs, ataxia, and isolated or multiple cranial neuropathies. 80% of DIPG cases exhibit the H3K27 mutation that has recently been re-classified as DMG.

A significant challenge in the investigation of treatment options is the scarcity of the tumour tissue, owing to the rarity and lethality of DIPG. Upon securing appropriate tissue cultures and accumulating sizeable cohorts, histone protein mutations and methylation changes responsible for DIPG can be isolated and identified.

Whilst most histologically similar adult lesions are safely surgically treated, the DIPG, camping in the pontine locus of the brainstem, evades resection due to its diffusely invasive nature. The implicit and high risk of morbidity and mortality amplify its poor prognosis, leaving surgery an unfeasible option.

Studies have reported a myriad of treatments, with varying efficacies. With radiotherapy (at doses of 54-60 Gy) and irradiation being among the best-tolerated and of potential benefit in controlling the initial flare; they've been approved for administration in children older than 3 years of age. Temozolomide, ritualistically used concurrently with RT, has rejected any claims to beneficence in DIPG management. Interestingly, as part of a 3-drug maintenance regime, temozolomide, irinotecan and bevacizumab (TIB) have proven to prolong survival in DIPG and pHGG patients in comparison to single agent regimens. Several reports also commented on the potency of Nimotuzumab with RT in outpatient settings.

Despite the apparent dismal prognosis, researches at the pre-clinical stage award hope of breakthroughs. HDAC inhibitors like Panobinostat (approved for multiple myelomas) with its promise of antitumorigenic effects pave the way for molecularly targeted clinical trials. Another propitious development is CBL0137, an anti-cancer compound derived from quinacrine, targeting the FACT complex. When used in combination with Panobinostat, studies report the prolonged survival of mice bearing DIPG ortho-grafts.

In conclusion, emergent approaches like nanotechnology utilising non-persistent gold NAs delivering cytotoxic Doxorubicin to DIPG cells, and SN-38 loaded nanoparticles modified with a peptide shuttle to penetrate the BBB, partially alleviate the disquiet of DIPG's median overall survival stagnating at 9-15 months for decades. With Focused Ultrasound in combination with microbubbles demonstrated as a safe and feasible technique to open BBB in a preclinical pontine glioma model, hopes to battle DIPG and emerge, thriving, from its hold are not farfetched.