Brain Tumour

Diffuse Intrinsic Pontine Gliomas

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Brain tumors are one of the most common paediatric solid tumours as well as the leading cause of childhood cancer-related deaths. The latest US statistics confirm that diffuse intrinsic pontine gliomas (DIPGs) constitute approximately 10-20% of paediatric brain tumours. Although epidemiological data for Australia is not published, the data founded in the US infers approximately 200-300 children per year are diagnosed with DIPG. DIPGs occur in all ages during childhood however the highest incidence is between the ages of 5 and 10. Median survival is typically less than one year from diagnosis, with a two year survival of less than 10%. DIPGs are typically grade II-IV astrocytic tumours which arise in the pons. The pons contains several vital centres (including pontine respiratory nuclei and nuclei of cranial nerves VVIII). Due to the anatomical position of the tumour, biopsy and surgical resection are not considered as diagnostic or therapeutic options prompting a dire need for therapeutic advances[1-4].

Clinical presentation.
DIPG patients often present with the classical brainstem signs such as cranial nerve dysfunction, long tract signs and ataxia either alone or in combination. Commonly reported symptoms are abnormal eye movements, asymmetric smile, clumsiness, difficulty walking, loss of balance, weakness as well as behavioral changes. The signs and symptoms may be present due to obstructive hydrocephalus resulting from expansion of the pons region. The symptoms are usually of acute onset and present for only 1-2 months prior to diagnosis[2].

Diagnosis
Diagnosis is made by neuroimaging based on characteristic findings. Magnetic resonance imaging (MRI) usually reveals a large expansile brainstem lesion although the tumour may extend into the midbrain or into the medulla. The lesions appear hypo- and hyper-intense on T1- and T2-weighted images, respectively, compared to normal brain. Contrast-enhancement is variable, but these tumors frequently do not enhance at diagnosis. The role of diagnostic biopsies has been controversial, with the majority of children not undergoing the procedure due to perceived increased morbidity and mortality however recent evidence suggests that the surgical risks may have been overestimated[5].

Molecular characteristics
Due to the paucity of biopsies, most of the genetic and molecular characterization of DIPGs comes from autopsies. Published reports have indicated that these tumours differ from other paediatric or adult gliomas and are characterized by gains of chromosomes 1q, 2p, 7p, 8q and 9q and losses in chromosomes 10q, 16q and 17p. At the gene expression level, DIPGs exhibit amplifications in the mRNA levels of PDGF receptor (*PDGFR*), hepatocyte growth factor receptor (*MET*), IGF receptor 1 (*IGF1R*), EGF receptors *(EGFR, ERBB4* and *EGFRv3*), poly-

ADP-ribose polymerase (*PARP*), as well as the increased expression levels of genes involved in phosphatidylinositide 3-kinase (PI3K) and retinoblastoma-associated protein (*RB*) pathways[6]. Another molecular abnormality associated with DIPGs is the recent discovery of a high frequency somatic mutation in the H3F3A gene, resulting in replacement of lysine 27 by methionine in its encoded histone H3.3 protein (H3.3K27M)[7]. This suggests that oncogenesis of DIPGs may be due to aberrant embryological development. Other studies have indicated that the hedgehog signaling pathway might be involved in the development of DIPG[8].

Treatment

Radiation therapy is the only therapeutic option observed to diminish neurological symptoms in patients with DIPG. Fractionated local irradiation improves symptoms in approximately 75% of newly diagnosed patients however the overall survival remains quite dismal. Many trials have attempted to increase the survival by combining radiotherapy with irradiation sensitisers such as platinum-based drugs and etoposide without success. Combination studies with temozolomide have also failed to show any benefit despite its success in adult glioblastoma. Furthermore clinical trials of PDGFR inhibitor imatinib have also failed to improve survival. Poor drug penetration as well as high expression of drug transporters has been considered to be responsible for the lack of effectiveness of chemotherapy regimes[3,9].

Future directions

It has only been shown in the last couple of years that DIPG cells can be cultivated from autopsy materials. For the first time, Monje et al successfully cultured DIPG cells as neurospheres (tumour spheroids) under culture conditions that allow the maintenance of a large $CD133^+$ stem cell population. These cells have also demonstrated tumour-initiating capacity in a xenograft mouse model. The neurosphere culture provides an ideal medium for *in vitro* drug screening and testing, as cells contained in neurospheres accurately reflect the tumour environment [8]. High-throughput screening strategies coupled together with xenograft animal models have the capacity to lead towards new effective treatments for DIPG. Furthermore new technologies based on convection enhanced delivery (CED) have shown promising pre-clinical activity on effectively distributing chemotherapeutics in the brain[10]. Ultimately, these recently established approaches will lead to the development on new therapeutic treatments that can be rapidly translated to clinical trials.

References

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