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Mini review

The Latest Understanding of Molecular Genetics, Diagnosis and Treatment of Childhood Malignant Glioma

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Abstract

Despite the histological resemblance of pediatric high-grade gliomas (PHGG) to their adult counterparts, they characterised by significant intra-tumor and inter-tumor heterogeneity and have distinct biological differences. Unlike the advances in the treatment of other malignancies, the clinical outcome of PHGG remains poor due to lack of significant progress in their current treatment protocols which typically comprise of surgery followed by radiotherapy and temozolomide. However, as our knowledge of the molecular biology of PHGG increases, novel approaches, such as molecular-based therapies have become new avenues that are required to be tested further in clinical trials. This review will critically appraise the latest advances in the understanding of the genetic dysregulations of PHGG and their role in disease pathogenesis, progression, and potential role in designing individualized molecular-based therapy with the view of improving patient's survival and quality of life.

Keywords: Pediatric high-grade gliomas; Molecular profiling of PHGG

Introduction

In children, central nervous tumours are the commonest solid malignancies and responsible for most cancer related fatalities. Gliomas arise from the astrocytes, the main glial make-up of the central nervous system (CNS). With incidence rate of 300 to 400 cases in Europe [1]. PHGG s are the most common malignant brain tumours in children and histologically are not distinguishable from the adult form [2]. However, unlike adult gliomas where the lesions are often in cerebral hemisphere, PHGG appears more diffusely in the brain with around 50% affecting the midline regions, especially the thalamus and the pons. About 60% of all childhood brain tumours are glioma and of those about 50% are high-grade gliomas. World Health Organization (WHO) defines PHGG as tumours of glial origin with a grade III or IV histology [2,3]. Glioblastoma multiforme (GBM) grade IV represents 15% of all paediatric brain tumours [3]. At a 5-year survival of less than 20%, PHGG represents a significant challenge to the scientific community [4]. There is a considerable need to develop effective, more tolerable therapies to improve survival and quality of life. The latter is especially important as the current therapies are associated with disabling neurotoxic complications such as neurocognitive dysfunction, hormonal disorders and neurosensory damage with only modest impact on overall survival (OS) [4]. Another significant challenge

is paucity of biospecimens and cellular models due to rarity and lethality of PHGG which in turn hinder designing of well-informed preclinical laboratory and genomic models to enhance treatment efficacy and understanding of predictors of long-term prognosis [5]. The analysis of more than 6000 PHGG of below 20 years old showed that in across all age group the locality of the tumour was the most important independent clinical marker of prognosis. However, in children <1 year the completeness of the resection was the main prognostic indicator [5]. The location of the tumours tends to be affected, although there are exceptions, by the disease age of onset. Older children often present with hemispheric lesions, however, midline and diffuse intrinsic pontine glioma (DIPG) affect younger and even more younger children, respectively. Midline and DIPG present particular challenges not only because of the aggressive nature of the disease but also due to surgical inaccessibility of the midline region and the brainstem [6]. Furthermore, the biological variability of PHGG explains the heterogeneity of these malignancies that have distinct genetic, epigenetic, and clinical subgroups [6].

There is an urgent need to develop molecular based treatment options for PHGG, as most chemotherapeutic and targeted therapy approaches in the past were hypothesised from adult GBM with disappointing results [7]. The past decade witnessed an increasing understanding in the relationship between genetic and epigenetic of PHGG on one hand and the age of onset, anatomical location, histopathological and radiological traits and clinical outcome on the other hand [1].

Molecular Profiling of PHGG And Its Implication on Management and Prognosis

Adulthood HGG is more frequent and has been more extensively studied compared to PHGG, their genetic and epigenetic profiles are different from PHGG. In adults there are two biological categories: secondary glioblastoma arising from pre-existing low-grade lesions, affecting adults < 40 years age and characterised by high mutation frequency of isocitrate dehydrogenase (IDH). As a small molecule protein IDH is involved key cellular pathways: glucose sensing, glutamine metabolism, lipogenesis, regulation of cellular redox status and mitochondrial oxidative phosphorylation [8]. Mutation in IDH triggers a number of cellular dysregulations. The secondary glioma group frequently harbour p53 mutation and PTEN loss. The second category is primary glioblastoma affecting older adults with most mutations (amplification) in epidermal growth factor receptor (EGFR) [9].

DNA methylation profiling, which is proven to be reproducible even from small and poor-quality biopsy material, enables researchers to classify PHGG to establish methylation and mutation status with the view of subtyping the tumours further with consequent implications to treatment and prognosis [10].

Histones are optometric proteins make the centre of the nucleosome around which DNA is wound. The histone tail directly interacts with DNA to control gene expression, via methylation and de-methylation or acetylation of the tail which silence or allow expression of the gene respectively. DNA methylation is catalysed by DNA methyltransferase (DNMT) enzymes, leads to silencing of a gene. Histone methylation is the change of specific amino acids in histone tail by adding of methyl groups [10].

The epigenetic driver of PHGG and DIPG is mutation in the gene encoding histone, the unique somatic mutation of PHGG and DIPG was confirmed by using genome-wide sequencing which showed a pattern of mutations in H3 histone, family 3A (H3F3A) and histone cluster 1, H3b (HIST1H3B), which encode the histone H3 variants H3.3 and H3.1 respectively [11]. About half of PHGG have somatic mutation affecting the gene encoding histone H3 and the other half with wild type H3 gene harbour a wide range of other mutations, ranging some of the highest mutation burden in human cancers to mutation in one driver gene [2]. The recurrent mutations in genes encoding histones H3.3 and H3.1 distinguish the childhood disease compared to the adult form [12].

In PHGG there's mutation in the histone tails at or next to these methylation or acetylation residues hence such mutation can lead to such a considerable alteration in gene expression. There are distinct mutations affecting the histone H3 gene. the lysine at position 27 (lysine to methionine (K27M)) and the glycine at position 34 (glycine to arginine (G34R) or glycine to valine (G34V)). The mutations strongly correlate with the anatomical location of the lesions, this suggests that different cell types are involved during brain organogenesis and indicates that the pathogenesis of DIPG is distinct from hemispheric lesions [1]. G34R/V is an activator of gene expression, its mutation up-regulates a number of oncogenes. Whereas K27M gene, is normally a suppressor gene, its mutation leads to removal of its silencing effect of the gene and subsequently overexpression of a range of oncogenes.

The Clinical Implications of The Type of the Mutation

78% of DIPGs harbour K27M gene mutation, which in turn, has two variants: H3.3 which affects the midline structures including thalamus, brainstem, cerebellum and spine and H3.1, which involves tumours in the brainstem. H3.1 variant is only found in DIPG in younger children [10,13-15]. This gene variation was reflected in 2016 WHO classification of a new variant of PHGG, called diffuse midline glioma H3K27M mutant, this classification is an example of integration of biological, histological and anatomical features [10]. G34R/V mutations occur in cerebral hemisphere in adolescent and younger adults (15%). G34R or G34V mutations are exclusively in H3F3A [16,17]. The mutation type impacts the prognosis is survival

median of 12 months for K27M; median of 24 months for G34R or G34V [10]. PHGGs lacking H3 or IDH mutations, (H3-/IDH-wild type) are a heterogenous disease entities, occurring throughout the CNS which a wide range of age of onset and clinical outcome [18]. Of those, pleomorphic xanthoastrocytoma (PXA) and low-grade gliomas (LGG) were identified using DNA methylation profiling. These tumours confer better OS compared to H3 or IDH mutant tumours. The PXA-like tumours often harbour deregulation of the MAPK pathway (BRAF V600E) with CDKN2A/CDKN2B deletion [19]. The following three subgroups of H3-/IDH-wild type with poor outcome have been identified: the largest subgroup is called pedGBM_MYCN" with high rate of MYCN amplification with co-amplification of the nearby ID2 gene on 2p.; the second subgroup "pedGBM_RTK1" harbours PDGFRA amplification and the final subgroup "pedGBM_RTK2" harbours EGFR amplification. MGMT promoter methylation in these subgroups, indicates a unique origin of PHGG compared to the adult form of the tumours. The high rate of unmethylated tumours accounts for resistance temozolomide or other alkylating drugs [14]. Moreover, infants under the age of 12 months with HGG have a low mutational burden with low frequency of chromosomal gains or losses. The more frequent events are gene fusions within chromosomes or cross chromosomes, particularly affecting receptor tyrosine kinases commonly NTRK1/2/3, ALK, ROS1 and MET. Infants with chromosomal fusions have better survival [14].

Molecular based Therapeutic Approach to PHGG

The identification of a specific molecular defect provides the opportunity to study targeted therap. The term low grade like PHGG refers to a tumour group that have the malignant characteristics of highgrade glioma mainly angiogenesis, but with a targetable pathway such as MAPK which harbours BRAF V600E that can be inhibited with a small molecule tyrosine kinase inhibitor (TKI) which can improve prognosis [15]. MAPK driven low grade like PHGG harbour increased immune infiltrates in their tumour microenvironment (TME), this increased immune cells infiltrates, mainly cytotoxic T lymphocytes (CTL) can be unleased to attach the cancer cells by using immune check point inhibitors such as program death 1 (PD-1), program death ligand 1 PD-L1) and Cytotoxic T-lymphocyte antigen 4 (CTLA4) [15]. Other targetable pathways include anti-angiogenesis (such as Bevacizumab), monoclonal antibodies to targeting EGFR and EGFR ligands, and drugs, that target mTOR pathway, such as Rapamycin.

The results from HERBY trial [16], showed that a subset of patients with hypermutated tumours (mismatch repair deficiency and somatic POLE/POLD1 mutations) and [PXA]-like, driven by BRAF_V600E or NF1 mutation tumours had more CD8-CTL infiltration of their TME and resulted in improved OS with addition of Bevacizumab compared to immune cold (fewer CD8 CTL infiltration of TME) Histone H3 mutant subgroups (hemispheric G34R/V and midline K27M.) .

Hypermutated tumours are associated with mutation in mismatch repair (MMR) germline gene and somatic POLE (DNA Polymerase Epsilon, Catalytic Subunit) genes which consequently results in elevated immune cell infiltration, and potential role for checkpoint inhibitors [16].

A surprising result of whole-exome sequencing of DIPG is identification of ACVR1 gene mutation, in 25% of patients [17]. ACVR 1 encodes serine/threonine kinase ALK2. This mutation is not known to affect any other human cancers, but cause a benign condition called fibrodysplasia ossificans progressiva (FOP), a severe and disabling musculoskeletal condition [18]. Developing an anti-ALK2 TKI is a priority to alter the deadly course of DIPG [19]. In vivo trials of two anti-ALK2 compounds (LDN-193189 or LDN-214177) were tested in orthotopic patient-derived xenografts a median benefit of 15 days in both cases in mice implanted with ACVR1 mutant DIPG cells with reduced tumour cellularity comparted to control mice. Despite the tumours lied behind intact blood brain barrier (BBB), the optimum intracellular drug contraction over sufficient duration was achieved. The same trial confirmed that prosurvival signalling in DIPG cells can be interrupted by ALK-2 inhibitors [19].

Moreover, in patients with ALK driving PHGG five anti-ALK drugs have either already confirmed efficacy or are in clinical trials, including Crizotinib and Ceritinib, and inhibitors with enhanced BBB permeability Ensartinib and Lorlatinib [19,20]. A subgroup of infant HGG bear mutations in the receptor tyrosine kinases ALK, ROS1, NTRK and MET [20]. The small molecule Larotrectinib, oral TRK inhibitor with high selectivity three NTRK receptor, showed efficacy in a phase 1 results from a multicentre, open label, studied in pre-treated PHGG with NRTK fusion. Encouraged by the above results, CONNECT 1903 trial is currently underway to test the safety and efficacy of Larotrectinib in upfront (treatment naïve) stetting in newly diagnosed PHGG with NTRK fusion [21].

Conclusion

PHGGs are developmental, aggressive and heterogenous group of diseases. Due to fundamental molecular differences between PHGG and adult HGG, PHGG cannot be understood exclusively by extrapolating data from adult HGG and we cannot simply translate findings from adult clinical trials to inform treatment of PHGG. Hence the need for research in exclusively paediatric population. DIPG requires a special attention as it is presenting an exasperating clinical conundrum due to its inaccessibility for surgical resection and as it has one of the deadliest disease courses in oncology. Better understanding of the genetic and epigenetic drivers of PHGG allowed profiling and subgrouping of the type of the tumour, integrating

these biological characteristics into other dataset namely the age of onset and anatomical location, compliment histological diagnosis. Immune checkpoint inhibitors and molecular based therapied have shown modest survival benefit with favourable safety profile. Future studies should focus on identifying robust biological and clinical markers to inform precision therapy and the role of the novel therapies in combination with irradiation, surgery and chemotherapy.

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