Pediatric Gliomas

Subjects: Oncology
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pLGGs or glioneuronal tumors (WHO grade 1 or 2) are highly heterogeneous entities. The most common single entity is pilocytic astrocytoma (0.91/100.000 patients age 0 to 19 years), followed by ganglioglioma, dysembryoplastic neuroepithelial tumor (DNET), and Grade 2 diffuse gliomas. High-grade gliomas of childhood are a histologically less heterogenic group of tumors with lower incidence compared to pLGGs (age-adjusted incidence, 0–19 years of age, is 0.26/100.000 without DIPGs). pHGGs consist of Grade 3 tumors like anaplastic astrocytomas (0.1/100.000 patients age 0 to 19 years) and anaplastic gangliogliomas, and Grade 4 tumors include GBM (0.18/100.000 patients age 0 to 19 years), DIPG (80% of brain stem tumors, which accounts for 15% of all CNS tumors), and gliomatosis cerebri, which is a highly infiltrative, special manifestation of HGG affecting multiple brain regions, not regarded as a separate subgroup any more.

Keywords: child ; classification ; central nervous system (CNS) tumor ; diffuse intrinsic pontine glioma (DIPG) ; glioma ; glioblastoma ; high grade glioma ; low grade glioma ; mitogen-activated protein kinase (MAPK) ; targeted therapy

1. Overview

The overall survival of pediatric gliomas varies over a wide spectrum depending on the tumor grade. Low-grade gliomas have an excellent long-term survival, with a possible burden of surgery, irradiation, and chemotherapy; in contrast, high-grade gliomas generally have a short-term, devastating lethal outcome. Recent advances in understanding their molecular background will transform the classification and therapeutic approaches of pediatric gliomas. Molecularly targeted treatments may acquire a leading role in the primary treatment of low-grade gliomas and may provide alternative therapeutic strategies for high-grade glioma cases in the attempt to avoid the highly unsuccessful conventional therapeutic approaches.

2. Malignant CNS

Malignant CNS (central nervous system) tumors are the second most common cancers of childhood, constituting 21% of cases. Gliomas are the most common type of CNS tumors, accounting for 35% of CNS tumors diagnosed in children between birth and 19 years of age [1]. Pediatric gliomas consist of WHO (World Health Organization) histological grade 1–2, low-grade gliomas (pLGG) (e.g., pilocytic astrocytomas, diffuse gliomas), accounting for 25% to 30% of all childhood CNS tumors, and WHO histological grade 3–4, pediatric high-grade gliomas (pHGG) (e.g., anaplastic astrocytoma, GBM (glioblastoma), DIPG (diffuse intrinsic pontine glioma)), accounting for one-third of pediatric gliomas [2]. Conventional therapies including neurosurgical intervention, radiotherapy, and chemotherapy often provide poor post-treatment quality of life, and survival of glioma patients is still devastating in several cases. In general, pLGGs have more than 90% overall survival rate; on the contrary, pHGGs have less than 10% long-term survival rate, despite the aggressive treatment regimens [3][4]. Recently, clarification of the molecular background of different gliomas has opened a new era in terms of their classification and treatment. In this review, this progress will be overviewed, offering a new hope for children with gliomas.

3. Epidemiology and Histological Classification

The latest WHO classification of CNS tumors was published in 2016, introducing some molecular parameters [5]. This classification considered growth pattern, tumor behavior, and shared genetic driver mutations to group different entities, in contrast to the previous WHO 2007 classification that was only focused on cellular origin [5]. The WHO 2016 classification only emphasized the significance of H3K27M mutation as a genetic driver mutation in pediatric gliomas, as IDH (isocitrate dehydrogenase) mutation or 1p/19q codeletion is extremely rare in childhood [6].

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neuroepithelial tumor (DNET), and Grade 2 diffuse gliomas. High-grade gliomas of childhood are a histologically less heterogenic group of tumors with lower incidence compared to pLGGs (age-adjusted incidence, 0–19 years of age, is 0.26/100.000 without DIPGs) [7]. pHGGs consist of Grade 3 tumors like anaplastic astrocytomas (0.1/100.000 patients age 0 to 19 years) and anaplastic gangliogliomas, and Grade 4 tumors include GBM (0.18/100.000 patients age 0 to 19 years), DIPG (80% of brain stem tumors, which accounts for 15% of all CNS tumors), and gliomatosis cerebri, which is a highly infiltrative, special manifestation of HGG affecting multiple brain regions, not regarded as a separate subgroup any more [7][8].

Recent advances in next-generation sequencing and array-based genomic platforms are leading to a necessary update of the WHO 2016 classification in the upcoming 5th edition of the WHO Classification of Tumors of the Central Nervous System in 2021 [9][10]. The fast advancements in biological sciences are promoting to the continuous discovery of promising biomarkers and new drug targets, and therefore an acceleration of the revision process is required. Accordingly, cIMPACT-NOW (Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy) was established in order to provide regular updates [10][11].

4. Activated Molecular Pathways in LGGs

In contrast to adult LGGs, the majority of pLGGs feature a unique activated signal transduction pathway, the RAS/MAPK (mitogen-activated protein kinase) pathway. In each case of pLGGs, only one variant genetic event could be observed, uniformly leading to the activation of the RAS/MAPK pathway. Therefore, pLGGs are regarded as “one-pathway diseases” [4]. The RAS/MAPK pathway can be affected by numerous inhibitor agents targeting different levels of the activated pathway. At present, these inhibitor agents are under investigation in different phases of human clinical trials. Whenever possible, it is essential to identify the exact genetic alteration by tissue sample analysis to initiate targeted therapy.

The most common tumor predisposition syndrome is neurofibromatosis type 1 (NF1), which is the consequence of a germline mutation of *NF1*, a tumor-suppressor gene located on chromosome 17. The *NF1* gene normally produces neurofibromin, a negative regulator of RAS protein. Failure of its suppression will activate RAS [12]. It is known that 10–15% of children with NF1 will develop optic pathway LGG and an additional 3–5% will present LGG outside of the optic pathway, the latter with worse prognosis [13][14]. LGG in NF1 could regress spontaneously, but in case of deterioration, as a first-line treatment, chemotherapy is applied (vincristine plus carboplatin or vinblastine in monotherapy) with strict avoidance of irradiation and without pretreatment biopsy [15][16][17]. In NF1, LGGs containing genetic alterations activating the RAS/MAPK or other pathways and HGG could also occur. Recently, CNS tumor biopsy has been highly indicated in NF1, at least for a focused testing of mutations and to choose the best treatment option [17].

The BRAF–KIAA1549 translocation is the most common molecular alteration in pLGG, which is the consequence of focal gains at 7q34, the location of the *BRAF* gene [4][18]. Due to the loss of the N-terminal regulatory domain of BRAF, downstream activation of the RAS/MAPK signaling pathway occurs [19]. BRAF–KIAA1549 is most commonly observed in pilocytic astrocytoma and in tumors arising in the posterior fossa [4]. Overall, 35% of pLGGs harbor this mutation [13]. The common cerebellar localization and a well-circumscribed behavior, especially in pilocytic astrocytoma, make the complete surgical removal amenable and predispose to an excellent outcome without additional treatment. LGGs harboring the BRAF–KIAA1549 translocation in other locations with incomplete surgical removal still have a better outcome compared to those lacking this genetic alteration [4][20]. Despite this, for tumors located in deep areas unfeasible for complete resection, progression could occur, and this may force additional therapy.

The BRAF V600E mutation in which a valine is replaced by glutamic acid at position 600 makes the MAPK/RAS pathway constitutively active. The BRAF V600E mutation as a molecular background for progression most commonly occurs in pleomorphic astrocytoma (77.8%), diffuse astrocytoma (43.5%), and ganglioglioma (49%) and is less common in pilomyxoid astrocytoma (13.3%), pilocytic astrocytoma (3%), and other LGGs, accounting for 15 to 20% of all pLGGs [21][22]. Supratentorial tumors, in contrast to cerebellar lesions, more commonly harbor BRAF V600E than the BRAF–KIAA1549 translocation [4]. pLGGs with the BRAF V600E mutation have a higher rate of local recurrence and a low overall survival rate after conventional treatment (irradiation, chemotherapy), despite their benign phenotype [21]. BRAF V600E-mutated pLGGs with the presence of the CDKN2A (Cyclin-Dependent Kinase Inhibitor 2A) deletion, more commonly described in pleomorphic xanthoastrocytoma, have a highly increased risk to transform to HGG in one or two decades [4][23]. As the co-occurrence of CDKN2A deletion has only recently been described, the real genetic alteration leading to progression is still under debate [24].

Activation of the RAS/MAPK pathway less frequently occurs at the receptor tyrosine kinase (RTK) level. FGFR1 (Fibroblast Growth Factor Receptor 1) plays a key role in signal transduction through the activation of its

intramembranous domain [25]. FGFR1 activating alterations are based on three different mechanisms: FGFR1 mutations (p.N546K, p.K656E), FGRFR1–TACC fusion, and FGFR1-TKD (tyrosine kinase domain) duplications [22][26][27]. All these mechanisms could be assigned to typical histological subtypes, but non-exclusively. FGFR1 mutations most frequently (20%) accompany DNTs, other glioneuronal tumors, and tumors in midline brain structures, but they rarely occur in pilocytic astrocytomas and oligodendrogliomas [4][13]. The FGFR1–TACC fusion most commonly occurs in pilocytic astrocytomas with a cystic lesion. FGFR1-TKD duplications, similarly to FGFR1 mutations, are most commonly (2–3%) present in DNTs and other glioneural tumors restricted to a cerebral hemisphere [4][13][26]. FGFR1 alterations commonly cause the upregulation of the PI3K/Akt/mTOR pathway [4]. FGFR1-mutated pLGGs have worse prognosis, but it is unclear if this is a consequence of reduced resection due to their midline localization or of the mutation itself [28]. NTRK (Neurotrophic Tyrosine Receptor Kinase) fusions, activating the same pathways described for FGFR1 activation, less frequently occur in LGG [4]. An ALK (Anaplastic Lymphoma Kinase) gene fusion has also been described in rare cases of gliomas, resulting in the activation of similar pathways. ALK fusion is mostly observed in infantile gliomas [29].

Other genetic alterations are also observed in pLGGs. MYBL1 and c-MYB have less significant effect on survival, and there are typical mutations of adult LGGs identified in older children (IDH1, IDH2, H3F3a), with incompletely identified prognostic significance [30]. Recent cIMPACT-NOW updates suggest creating a “pediatric-type” diffuse glioma group comprising histologically diffuse gliomas with BRAF V600E mutation (without CDKN2A/B homozygous deletion), FGFR1 alteration, or MYB and MYBL1 rearrangement [31].

5. Conclusions

The recent advances in understanding the molecular background of pediatric gliomas are facilitating the application of effective drugs targeting the Ras/MAPK pathway, with fewer side effects in the case of pediatric low-grade gliomas, thus substituting harmful chemotherapy and irradiation. In the case of pediatric high-grade gliomas, understanding the molecular mechanism sustaining tumor progression and implementing recent advances to overcome the BBB may open novel therapeutic windows to treat these devastating diseases. The most promising approach is based on the highly immunogenic features of high-grade gliomas, which may be utilized by the reactivation of the ineffective self-protecting immune mechanisms or by applying other mechanisms such as CAR-T cell therapy or vaccination.

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