Innovative therapy concepts for pediatric brain tumors

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Summary In recent years, novel insight into molecular mechanisms has allowed the identification of drug targets for various pediatric brain tumors. The aim of this article is to give an overview of new treatment options in neurofibromatosis type 1 (NF1), novel tyrosine kinase inhibitors that target oncogenic gene fusions in pediatric brain tumors, and antiangiogenesis as promising therapy especially in recurrent medulloblastoma.

Keywords NF1 · BRAF · Oncogenic fusion proteins · Antiangiogenesis

Introduction

The survival rates of pediatric brain tumor patients improved constantly during the end of the 20th century. This was mainly due to technological advances in imaging, neurosurgery and radiotherapy, as well as the use of combination chemotherapy. In the last two decades, however, outcome rates remained rather static, reflecting our lack of knowledge of the underlying molecular mechanisms of different pediatric brain tumors.

In recent years, molecular characterization has massively changed the landscape of pediatric central nervous system (CNS) malignancies [1]. This novel insight into molecular mechanisms also allows the identification of drug targets in different pediatric brain tumors. It is therefore realistic that the near future will bring further advancement in the treatment of these malignancies.

Targeting the pathway in low grade glioma by MEK inhibition

Neurofibromatosis type 1 (NF1) is the most common genetic tumor predisposition syndrome associated with the development of CNS tumors with an incidence of 1 in 3000. In this monogenetic disease, the NF1 gene and consecutively the tumor suppressor neurofibromin (as regulator of RAS) is altered, leading to uncontrolled RAS-mitogen-activated protein kinase (RAS/MAPK) pathway activation upon damage of the second allele (second hit). Low grade gliomas (LGG) are the most frequent CNS malignancies associated with NF1 and are almost exclusively driven by this mutation [2]. Molecular analysis of sporadic LGGs has revealed that they also unanimously harbor alterations in the MAPK pathway [3].

While LGG is associated with a generally high overall survival rate and many patients can be cured by surgery alone, other LGGs necessitate nonsurgical treatment, the gold standard being chemotherapy with carboplatin and vincristine [4]. Some patients with LGG suffer multiple relapses and response to cytotoxic therapy diminishes with each progression [5]. Therefore, alternative therapy options are needed.

BRAF and MEK inhibitors were developed for the treatment of BRAF-mutated malignant melanoma. The MEK inhibitor selumetinib was evaluated in a pediatric trial for inoperable NF1-associated plexiform neurofibroma and demonstrated high volumetric response rates with tolerable side effects [6, 7]. The use of the first generation BRAF inhibitor sorafenib in LGG was associated with rapid tumor progression, finally proven to be caused by a positive feedback loop in cell signaling [8]. Hence consecutively, downstream inhibition by MEK inhibitors was attempted. Selumetinib was proven to be effective in a phase 1 trial and a more comprehensive phase 2 trial could underline these re-
sults [9, 10]. Prolonged progression-free survival (PFS) rates could be achieved, and in optic pathway glioma, improved visual outcomes were reported. Specifically, in the NF1 subgroup, a high partial response rate of 36% (60% stable disease) was observed with a 96% 2-year PFS. This can be considered as a class effect of MEK inhibitors, as similar results have been shown in patients treated with trametinib [11]. Yet, the efficacy of these agents remains to be proven in a first-line setting regarding long-term effects and side effects compared to standard of care chemotherapy. Such trials have already opened or will do so in the near future (e.g., LOGGIC Europe. ACNS1831). Possible side effects of MEK inhibition include frequently skin toxicities (in about 60% of patients) like acne or paronychia that are most often manageable by local therapies, and less often fatigue, gastrointestinal symptoms, CK elevation as well as rare cases of retinal detachment or left ventricular dysfunction [12–14]. BRAF-V600E-mutated pediatric LGG may not be as chemotherapeutic sensitive as other LGG [15]. The combination of the selective BRAF V600E inhibitor dabrafenib and the MEK inhibitor trametinib were proven effective in this subset of patients [16].

**Novel tyrosine kinase inhibitors target oncogenic gene fusions**

Apart from oncogenic signaling activation by loss of NF1, also somatic alterations, most prominently mutations or fusions involving BRAF, have been described in pediatric high-grade gliomas [17]. More recently, fusions of other signaling molecules, such as NTRK1/2/3, ALK, MET, or ROS1, have been discovered by large-scale high-throughput screens [18–20]. Importantly, as alterations in these oncogenes are also found in adult cancer types, inhibitors targeting these receptors have already undergone clinical development involving the pediatric population [21]. Preclinical analyses of our group and others demonstrate good effects of these inhibitors against fusion-positive cancer cells corroborating first results within ongoing clinical trials as well as selected case reports [19, 20, 22].

Currently available inhibitors include crizotinib, larotrectinib and entrectinib, which are approved by European Medicines Agency (EMA) and US Food and Drug Administration (FDA), as well as the second-generation inhibitors selitrectinib and repotrectinib, which are in clinical development [21]. It has to be considered that these inhibitors show different specificity for the aforementioned therapy targets and are only approved within certain indications, in particular in the pediatric population (Table 1).

Only a minor proportion of high-grade gliomas harbor these specific gene fusions, underlying that comprehensive molecular profiling of pediatric brain tumors at an early timepoint is required in order to facilitate detection of these therapeutic targets. With respect to brain tumors, penetration of the blood–brain barrier is also of particular interest. In general, penetration of crizotinib to the central nervous system is considered to be poor, but still efficacy in pediatric brain tumors has been described [19]. For the newer compounds larotrectinib and entrectinib both have demonstrated effects against pediatric brain tumors in a clinical setting [20, 22]. These novel compounds are generally well tolerated, only a minority of patients require dose modifications or discontinuation of treatment [21]. With respect to blood–brain barrier penetration, first analyses point towards a more favorable profile of entrectinib, as animal studies have demonstrated higher penetration of tumor tissue [23]. In addition, it was recently shown that entrectinib also efficiently enters the cerebrospinal fluid [22]. Still, it has to be considered that safety profiles in the pediatric population, and in young children in particular, are currently more established for larotrectinib, which is also reflected by the approval independent of age. Response to these inhibitors is usually quick and frequently also for a prolonged period of time [21, 22]. Still, various resistance mechanisms have been described in the adult population, including resistance mutations, and second-generation inhibitors are already being developed. Less is known about resistance mechanisms in pediatric brain tumors, but we have recently described NF2 mutation and activation insulin receptor (INSR) signaling as potential resistance mechanisms [23]. The main ongoing pediatric trials with targeted drugs are listed in Table 2.

**Antiangiogenic treatment**

Medulloblastoma is a highly malignant embryonal tumor arising in the cerebellum. By using multimodal therapy that includes surgical resection, craniospinal irradiation and combination chemotherapy, approximately 70% of children achieve long-term survival, but with sometimes devastating sequelae [24].

### Table 1 Targeted inhibitors for oncogenic gene fusions in pediatric brain tumors (adapted from [17])

| Inhibitor     | Targets                                      | Approval                                      |
|---------------|----------------------------------------------|-----------------------------------------------|
| Crizotinib    | ALK, MET, NTRK1/2/3 (minimal), ROS1          | ALK/ROS1 altered (lung cancer)                |
| Larotrectinib | NTRK1/2/3                                     | NTRK fusion-positive tumors (any age)         |
| Entrectinib   | ALK, NTRK1/2/3, ROS1                         | NTRK fusion-positive tumors (>12 years), ROS1 altered (lung cancer) |
| Selitrectinib | NTRK1/2/3 (including most mutations)         | –                                             |
| Repotrectinib | ALK, ROS1, NTRK1/2/3 (including most mutations) | –                                             |
In recent years, tremendous progress in molecular genetics has provided significant advancements in our understanding of medulloblastoma. There is now consensus on four distinct molecular subgroups: wingless (WNT), sonic hedgehog (SHH), group 3, and group 4 [25]. Recently, further subgroup heterogeneity has been defined [26]. These molecular groups have already formed the basis of the current clinical treatment protocol PNET5 (ClinicalTrials.gov Identifier: NCT02066220), where WNT-medulloblastomas are treated with reduced radio- and chemotherapy.

Despite the favorable outcome after the initial diagnosis, patients with relapsed medulloblastoma have a very poor prognosis, whether treated with conventional chemotherapy, high-dose chemotherapy with stem cell rescue, irradiation or combinations of these modalities [27, 28].

Angiogenesis, the formation of new blood vessels, is an important component of normal physiological processes such as wound healing. Moreover, tumor growth and metastases depend on the formation of new blood vessels [29].

The frequent delivery of different drugs, referred to as metronomic or antiangiogenic therapy, targets the endothelial cells while reducing the toxicity associated with standard dose chemotherapy. Antiangiogenic therapy inhibits vascular formation, thereby inhibiting tumor progression indirectly [30, 30].

Various trials have demonstrated that antiangiogenic drugs are generally insufficient as single agents, a combination of different agents is considered to be more promising [31].

We used an antiangiogenic multidrug regime, consisting of bevacizumab, thalidomide, celecoxib, fenofibrate, etoposide, and cyclophosphamide. All of these drugs have been shown to have antiangiogenic effects [32–37]. Additionally, we administered intraventricular therapy (etoposide and cytarabine), since the cerebrospinal fluid (CSF) compartment is not targeted with antiangiogenic therapy. With this regime, we achieved promising results, especially in recurrent medulloblastoma [38]. Three of the seven patients with recurrent medulloblastoma in our series achieved long-term survival [38]. Therapy was generally well tolerated, and toxicities were manageable. The most common toxicities were hypertension, a well-described side effect of bevacizumab, chemical arachnoiditis occurring after intraventricular liposomal cytarabine, and the patients were more prone to infections because of the immunosuppression. [38].

Our results suggested that this antiangiogenic drug combination may be beneficial for patients with recurrent medulloblastoma. Further investigation with a formal phase II study is in progress (Metronomic and Targeted Anti-angiogenesis Therapy for Children with Recurrent/Progressive Medulloblastoma (MEMMAT); ClinicalTrials.gov Identifier: NCT01356290).

Conclusion

The information of the genomic mechanisms has revolutionized our understanding of the underlying pathogenesis of pediatric brain tumors. Oncogenic gene fusions offer novel therapeutic opportunities for pediatric brain tumors and have already entered clinical practice. Open questions remain regarding the optimal timepoint of treatment initialization, duration of treatment, combination with other treatment modalities and avoidance of resistance. The laboratory-based findings will define a path for future clinical studies. The main challenge will be to design protocols with international collaboration that include molecular information, to improve the survival rate while minimizing toxicities.

Take-home message

- Targeting the BRAF pathway in inoperable NF1-associated tumors is a promising option.
- Oncogenic gene fusions offer novel therapeutic opportunities.
- Antiangiogenic combinations may be beneficial for recurrent medulloblastoma.
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Conflict of interest A.A. Azizi, J. Gojo and A. Peyrl declare that they have no competing interests.

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short review

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