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Upfront treatment with mTOR inhibitor everolimus in pediatric low-grade gliomas: A single-center experience

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Abstract

Pediatric low-grade gliomas (pLGGs) are the most frequent brain tumor in children. Adjuvant treatment, consisting in chemotherapy and radiotherapy, is often necessary if a complete surgical resection cannot be obtained. Traditional treatment approaches result in a significant long-term morbidity, with a detrimental impact on quality of life. Dysregulation of the mitogen-activated protein kinase (MAPK) pathway is the molecular hallmark of pLGGs and hyperactivation of the downstream mammalian target of rapamycin (mTOR) pathway is frequently observed. We report clinical and radiological results of front-line treatment with everolimus in 10 consecutive patients diagnosed with m-TOR positive pLGGs at the Bambino Gesù Children's Hospital in Rome, Italy. Median duration of treatment was 19 months (range from 13-60). Brain

Abbreviations: AG, angiocentric glioma; BR, best radiological response; BSA, bovine serum albumin; CNS, central nervous system; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DNET, dysembryoplastic neuroepithelial tumor; EPIC, HumanMethylation EPIC BeadChip; FFPE, formalin-fixed paraffin-embedded; GG, ganglioglioma; IHC, immunohistochemistry; IMP, improvement; MAPK, mitogen-activated protein kinase pathway; MRI, magnetic resonance imaging; mTOR, mammalian target of rapamycin; NF1, neurofibromatosis type 1; NS, Noonan syndrome; PAs, pilocytic astrocytomas; PD, progressive disease; pLGGs, pediatric low-grade gliomas; p-mTOR, phosphorylated mTOR; PR, partial response; RT, room temperature; SD, stable disease; SEGA, sub-ependymal giant astrocytoma; SIOP, International Society of Paediatric Oncology; TS, tuberous sclerosis.

magnetic resonance imaging showed stable disease in 7 patients, partial response in 1 and disease progression in 2. Therapy-related adverse events were always reversible after dose reduction or temporary treatment interruption. To the best of our knowledge, this is the first report of everolimus treatment for chemo- and radiotherapy-naïve children with pLGG. Our results provide preliminary support, despite low sample size, for the use of everolimus as target therapy in pLGG showing lack of progression with a manageable toxicity profile.

KEYWORDS

everolimus, MAPK pathway, mTOR, pediatric low-grade gliomas

1 | INTRODUCTION

Pediatric low-grade gliomas (pLGGs) represent the most common tumors of the central nervous system (CNS). Median age at diagnosis is around 6 to 8 years, and about 7% of patients are younger than 1 year of age.[1,2] Histologically, they are a heterogeneous group of Grade I and II tumors of glial origin, according to the latest version of 2016 WHO classification.[3]

Surgery is the mainstay of pLGG treatment. Complete resection of the tumor alone is feasible in 60% of cases,[4] and a diagnostic biopsy is possible in over 95%.[5] However, unresectable residual tumors might have a tendency to progress clinically and radiologically, requiring further treatment[6] in a percentage ranging from 25% to 35% of patients.[4] Adjuvant treatment is based on chemotherapy and the standard of care is the scheme combining carboplatin and vincristine.[7] Well-known morbidities related to chemotherapy consist of neuropathy, myelosuppression and consequent high risk of infections requiring hospitalization and a worsening of quality of life, ototoxicity, nausea and vomiting, carboplatin hypersensitivity reaction.

Radiation therapy is reserved to 30% of patients, particularly in certain scenarios like older children or after failure of multiple treatment lines.[8] Despite their overall good prognosis, pLGGs can cause significant long-term morbidity due to the disease and its treatments. Particularly, radiotherapy may cause a decline in neurocognitive function, vasculopathy and malignant transformation of primary tumor. All these sequelae have a loud for patients, their families and society. Therefore, side effect reduction and quality of life preservation are increasingly been valorized as the main goal of any proposed therapy.

The main molecular alterations shown by LGG relate to the activation of the mitogen-activated protein kinase pathway (MAPK) pathway. In the majority of these cases, either duplication or point mutations of the BRAF gene[9] are identified, allowing to consider signal transducers belonging to the MAPK pathway as potential target for therapy. Patients negative for *BRAF* mutations/rearrangements, instead, are not eligible for these treatments. Interestingly, evidence of mechanistic target of rapamycin (mTOR) iper-activation was observed in pLGGs associated with syndromic conditions, as tuberous sclerosis (TS) and neurofibromatosis type 1 (NF1) which has paved the way toward the clinical use of mTOR inhibitors, like everolimus.[10-16]

What's new?

Traditional therapeutic approaches for pediatric low-grade glioma (pLGG) center on surgery and radiotherapy. Radiotherapy in particular, however, can have long-term, detrimental impacts on patient health. Here, the authors investigated the use of everolimus as a post-surgical, front-line targeted therapy in a group of 10 chemo- and radiotherapy-naïve children with pLGGs harboring alterations in mTOR signaling pathways. Front-line everolimus therapy was associated with a high rate of clinical response, with disease stabilization in the majority of patients. Adverse effects were resolved following temporary everolimus interruption. These preliminary findings warrant further investigation of everolimus as a targeted therapeutic strategy for mTOR-positive pLGG.

However, activation of the mTOR pathway is not restricted to pLGGs associated with the aforementioned conditions. In fact, mTOR activation has been reported in sporadic Pilocytic Astrocytomas (PAs), the most frequent pLGG histotype, as well as in in vitro primary models of pLGG belonging to less frequent histological variants, such as angiocentric glioma (AG), dysembryoplastic neuroepithelial tumor (DNET) and ganglioglioma (GG).[11,12]

In the current study, we present preliminary results on the first ever reported use of everolimus as upfront postsurgery treatment in mTOR/phospho-mTOR-positive pLGGs.

2 | MATERIALS AND METHODS

2.1 | Study design

This is a retrospective, single-center study to evaluate the efficacy of everolimus as front-line therapy for pLGGs after surgery.

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