

Introduction

Activation of the mitogen activated protein kinase (MAPK) pathway through the BRAF oncogene and/or loss of the tumor suppressor neurofibromin 1 has been found to contribute to the pathogenesis and tumorigenesis of pediatric low-grade gliomas (LGG). Similarly, loss of neurofibromin is associated with the formation of neurofibromatosis type 1- associated plexiform neurofibromas (PN). Therefore, targeted therapy inhibiting the MAPK pathway with the mitogen-activated protein kinase kinase (MEK) inhibitor trametinib can augment traditional chemotherapy, radiotherapy, and surgical resection practices.

Methods

A retrospective chart review was conducted using the electronic medical records at Children's Hospital Colorado (CHCO) to identify pediatric patients (age \leq 18 years old) with low grade gliomas (LGG) and/or plexiform neurofibromas (PN) who were treated with trametinib from 2015 – 2020. Data collected included patient demographics, location of the lesion, tumor molecular changes, NF1 status, best response to trametinib, duration of trametinib therapy, reason to discontinue trametinib therapy, and toxicities possibly attributed to trametinib therapy.

Results

Thirty patients (60% male) were identified. Thirteen (43%) had LGG only, fifteen (50%) had PN only, and two (7%) had both LGG and PN. The most common LGG location was the optic pathway/hypothalamus (67%), followed by the thalamus/brainstem (13%), spine (13%), or multifocal sites (7%). The most common PN location was the face (47.2%), followed by the neck (17.6%), trunk (17.6%), or multiple sites (17.6%). Of the

fifteen patients with LGG, eight (53.3%) had mutations in BRAF or NF1. The median duration of trametinib therapy was 2 years (range 0.7 – 3.6 years). The most common toxicities included diarrhea, paronychia, and rash. No cardiac or ophthalmologic toxicity were reported in any of the patients. Of the patients with LGG, eight (53%) had stable disease (SD) and seven (47%) had partial responses (PR) to trametinib. Of the patients with PN, eleven (65%) had stable disease (SD) and six (35%) had partial responses to trametinib. Thirteen (43%) discontinued trametinib due to completion of planned treatment duration, eleven (37%) were still on therapy at the time of data censor, three (10%) discontinued due to toxicity, two (7%) discontinued due to progression of disease, and one (3%) was lost to follow-up.

Conclusions

Although this retrospective study cannot fully characterize clinical efficacy, the majority of patients with LGG or PN demonstrated at least stable disease, if not partial responses, with trametinib treatment. Additionally, very minimal short-term toxicities were reported, and, notably, no cardiac or retinal toxicities were found.