PubMed

Format: Abstract

Pediatr Blood Cancer. 2018 Mar 7. doi: 10.1002/pbc.27035. [Epub ahead of print]

Phase 1 trial, pharmacokinetics, and pharmacodynamics of dasatinib combined with crizotinib in children with recurrent or progressive high-grade and diffuse intrinsic pontine glioma.

Broniscer A[1,2], Jia S, Mandrell B, Hamideh D, Huang J, Onar-Thomas A, Gajjar A, Raimondi SC, Tatevossian RG, Stewart CF.

1 Department of Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee.
2 Department of Pediatrics, University of Tennessee Health Science Center, Memphis, Tennesssee.

Abstract

BACKGROUND: Progressive/recurrent high-grade and diffuse intrinsic pontine gliomas (DIPGs) are fatal. Treatments targeting molecular pathways critical for these cancers are needed.

METHODS: We conducted a phase 1 study (rolling-six design) to establish the safety and maximum tolerated dose (MTD) of dasatinib, an oral platelet-derived growth factor receptor A (PDGFRA) inhibitor, and crizotinib, an oral c-Met inhibitor, in such patients. Pharmacokinetics of both agents were performed. Biomarkers of cellular pathway activation in peripheral-blood mononuclear cells (PBMC) were evaluated before and after administration of dasatinib. PDGFRA and MET amplification, and PDGFRA mutations were studied in tumor samples.

RESULTS: Twenty-five patients were enrolled in this study (median age: 11.9 years). Eleven patients had DIPG. Glioblastoma accounted for 40% of cases. Dasatinib at 50 mg/m^2 and crizotinib at 130 mg/m^2 or 100 mg/m^2 were poorly tolerated when administered twice daily. Drug administration was then switched to once daily. Dasatinib administered at 50 mg/m^2 and crizotinib at 215 mg/m^2 once daily was the MTD. Dose-limiting toxicities consisted of diarrhea, fatigue, proteinuria, hyponatremia, rash, and grade 4 neutropenia. Only two patients received therapy for at least 6 months. No objective radiologic responses were observed. Pharmacokinetics of dasatinib and crizotinib were comparable to previous studies. A statistically significant decrease in the ratio of p-AKT/total AKT in PBMC occurred after dasatinib administration. PDGFRA and MET amplification were found in four and two cases, respectively. Only one of 10 tumors harbored a PDGFRA mutation.

CONCLUSIONS: This drug combination was poorly tolerated and its activity was minimal. We do not recommend further testing of this combination in children.

KEYWORDS: PDGFRA; c-Met; children; crizotinib; dasatinib; diffuse intrinsic pontine glioma; high-grade

glioma

PMID: 29512900 DOI: 10.1002/pbc.27035