Targeted therapy for pediatric low-grade gliomas and plexiform neurofibromas with trametinib

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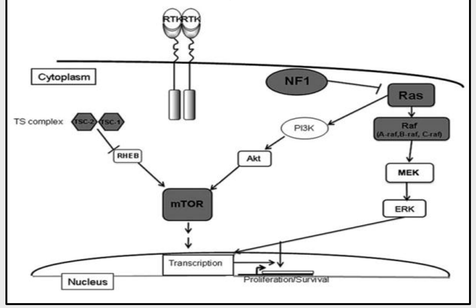
Introduction

Activation of the mitogen activated protein kinase (MAPK) pathway through the BRAF oncogene and/or loss of tumor suppressor NF1 contributes to the tumorigenesis of pediatric low-grade gliomas (LGG) and neurofibromatosis type 1-associated plexiform neurofibromas (PN).

By inhibiting the MAPK pathway with the MEK1/2 inhibitor, trametinib, we aimed to study tumor responses, adverse effects, and opportunities to augment standard of therapy.



Materials and methods

Retrospective, IRB-approved (COMIRB #18-1383) chart review was performed at Children's Hospital Colorado (2015 - 2020) to identify patients ≤ 18 yo with LGG and/or PN treated with trametinib. Demographics, tumor molecular changes, NF1 status, best response to trametinib, therapy duration, reason to discontinue, and possible toxicities attributed to trametinib were collected.

Results

Table 1: Patient characteristics	
# of pts, n (%)	30 (100%)
Age at initiation of trametinib	
Median	9.6 y
Range	2.0 – 18.8 y
Tumor type, n (%)	
LGG	13 (43%)
PN	15 (50%)
Both	2 (7%)
BRAF or NF1 LGG molecular mutations, n (%)	
Yes	8 (53.3%)
No	5 (33.3%)
Unknown	2 (13.3%)

Table 2: Treatment Outcomes	
Duration of therapy	
Median	2.0 y
Range	0.7 – 3.6 y
Best LGG response	
Stable Disease (SD)	8 (53%)
Partial Response (PR)	7 (47%)
Best PN response	
Stable Disease (SD)	11 (65%)
Partial Response (imaging or clinical)	6 (35%)
Reason to discontinue	
Completed	13 (43%)
On therapy at censor	11 (37%)
Toxicity	3 (10%)
Progression	2 (7%)
Lost to follow-up	1 (3%)

Table 3: Common toxicities	All (n = 30)	LGG (n = 14)	PN (n = 16)
Diarrhea	5 (17%)	4 (29%)	1 (6%)
Paronychia	15 (50%)	8 (57%)	7 (44%)
Rash	27 (90%)	11 (79%)	16 (100%)
Mucositis	1 (3%)	0 (0%)	1 (6%)
Pericardial effusion	1 (3%)	0 (0%)	1 (6%)
Wound breakdown	1 (3%)	0 (0%)	1 (6%)

Conclusions

Most patients maintained at least stable disease with trametinib treatment.

Trametinib was largely well tolerated. Only minimal short-term toxicities (i.e. rash, paronychia) were found with the administration of trametinib even after years of treatment.

Limitations

Study is limited by retrospective nature and small sample size.

Prospective clinical trials are needed to further characterize tumor responses and adverse events.

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Conflicts of Interest Declaration

All authors have no conflicts of interest to declare.