DOI: 10.1002/hsr2.1841

CORRESPONDENCE

Health Science Reports Open Access WILEY

Dabrafenib plus Trametinib: A breakthrough in pediatric low-grade glioma therapy

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Abstract

Background and Aims: Pediatric-type low-grade gliomas (pLGGs) are the most common solid tumors in children, with v-raf murine sarcoma viral oncogene homolog B (BRAF) mutations playing a significant role in their development. Dabrafenib and trametinib are targeted therapies that are recently approved by Food and Drug Administration for pediatric patients with pLGG harboring a BRAF V600E mutation.

Body: This study emphasizes the role of Dabrafenib and Trametinib in pLGG. A multicenter Phase I/II trial demonstrated the superior efficacy of dabrafenib plus trametinib (D+T) compared to carboplatin plus vincristine (C+T), with higher overall response rates, clinical benefit rates, and longer progression-free survival. The safety profile of dabrafenib plus trametinib (D+T) was favorable, with fewer discontinuations and adverse events compared to the control group.

Conclusion: The introduction of D+T as a targeted therapy represents a significant advancement in the management of pLGG, necessitating further investigations to understand its long-term consequences and optimize patient care.

KEYWORDS

dabrafenib, pediatric low-grade glioma, pLGG, trametinib

Central nervous system tumors are the most prevalent solid tumors in children, occurring at a rate of approximately 5.4−5.6 cases per 100,000 in the United States. Among them, pediatric-type low-grade gliomas (pLGG), which are classified as Grade I and II by WHO, are the most common, accounting for about 1.3−2.1 per 100,000 cases in the United States.[1,2] pLGGs are a diverse group of tumors with different locations, histologic subtypes, ages at diagnosis, and clinical features. Some tumors mainly consist of glial cells, such as astrocytes and oligodendrocytes, while others have a mix of both glial and neuronal cells.[3,4]

Genetic alterations causing continuous activation of the mitogen-activated protein kinase (MAPK) pathway are found in various pediatric cancers, indicating the potential for improved outcomes with targeted therapies.[5] v-raf murine sarcoma viral oncogene homolog B (BRAF) is the most commonly mutated kinase in cancer[6] and BRAF mutations are commonly found in pLGGs which lead to abnormal activation of cell signaling pathways. The most prevalent BRAF mutation in pLGGs is the V600E mutation constituting 90% of all BRAF mutations.[7] pLGGs with BRAF V600 mutation show limited response to standard chemotherapy and an increased risk of transforming into high-grade glioma (HGG). Additionally, these patients experience poor progression-free survival (PFS), highlighting the need for alternative treatment approaches.[8]

Dabrafenib (Tafinlar) in combination with trametinib (Mekinist) was approved by the Food and Drug Administration on March 16, 2023, for pediatric patients aged 1 year and older with LGG harboring a BRAF V600E mutation. This is considered first-line systemic therapy for pediatric patients with BRAF V600E-mutated LGG.[9] Upon activation by RAS, BRAF triggers the activation of MEK1 and MEK2 through phosphorylation, leading to the activation of ERK1 and ERK2 which regulates cellular signaling.[10] Dabrafenib specifically targets and inhibits the mutated BRAF protein, while trametinib inhibits MEK1 and MEK2[11] thereby disrupting the aberrant MAPK/ERK pathway activation in cancer cells. Both drugs demonstrate extended PFS compared to chemotherapy drugs.[12,13]

The efficacy of the combination was assessed in a multicentre Phase I/II open-label trial in patients with pLGG. The trial randomized a total of 110 patients with progressive disease after surgery or nonsurgical patients who required systemic treatment. They were assigned in a 2:1 ratio to receive either dabrafenib plus trametinib (D + T) or carboplatin plus vincristine (C + T) using different dosing based on age. The primary endpoint of the trial was the overall response rate (ORR) while the secondary endpoints included investigator-assessed ORR, clinical benefit rate (CBR), duration of response, time to response, PFS, overall survival, and safety evaluation. The trial demonstrated superior efficacy in the D + T group compared to the C + T group. The independently assessed ORR was higher with D + T (47% vs. 11%), as was the CBR (86% vs. 46%). Median PFS was significantly longer with D + T (20.1 vs. 7.4 months), with higher 12-month Kaplan–Meier PFS rates (67% vs. 26%).[14]

In terms of safety, no deaths related to LGG occurred in the D + T group, while one death was reported in the C + T group. Patients receiving D + T had lower rates of discontinuation due to adverse events (4% vs. 18%) compared to those in the C + V group. The most common adverse events observed with D + T were pyrexia (68%), rash (54%), headache (40%), vomiting (34%), musculoskeletal pain (36%), fatigue (31%), dry skin (31%), diarrhea (30%), nausea (26%), epistaxis and other bleeding events (25%), abdominal pain (24%), and dermatitis acneiform (23%). The most common (>2%) Grade 3 or 4 laboratory abnormalities were decreased neutrophil count (20%), increased alanine aminotransferase (3.1%), and aspartate aminotransferase increased (3.1%).[14]

Notably, an ongoing Phase III trial is investigating the efficacy of selumetinib, a MEK inhibitor, comparing its performance to the standard C + V treatment, in patients aged 2–21 years, with Neurofibromatosis 1 (NF1) associated low-grade glioma. This study also aims to evaluate whether selumetinib outperforms C + V in enhancing vision for individuals with LGG affecting the optic pathway (ClinicalTrials.gov ID: NCT03871257). The ongoing FIREFLY-2 Phase 3 trial marks a significant advancement in pediatric oncology, focusing on LGG with activating RAF alterations. Utilizing a 2-arm, randomized, open-label design across global centers, the study aims to evaluate DAY101, highly selective type 2 pan-RAF kinase inhibitor, monotherapy against standard chemotherapy, in patients aged up to 25 years, addressing a critical need for effective treatments in this subset (ClinicalTrials.gov ID: NCT05566795). These ongoing trials would enhance the robustness and hold promise for advancing precision medicine in pediatric oncology. These trials underscore the need for continued exploration of targeted therapies and precision medicine. Close monitoring of both efficacy and safety in real-world scenarios is imperative to determine their potential as front-line treatments. The approval of D + T as a targeted therapy represents a significant advancement in the management of pLGG. Further trials should be conducted to investigate the long-term outcomes and effects of D + T. These evaluations will provide valuable insights into the long-term consequences of therapy and help guide supportive care strategies to mitigate any adverse effects.

AUTHOR CONTRIBUTIONS

Marrium Sultan Dar: Conceptualization; writing—original draft; writing—review and editing. **Nayab Shahid**: Writing—original draft. **Arisha Waqas**: Writing—original draft. **Yumna Arif Baig**: Writing—original draft. **Aimen Waqar Khan**: Writing—review and editing. All authors have read and approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are included within the paper. Marrium Sultan Dar had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

TRANSPARENCY STATEMENT

The lead author Aimen Waqar Khan affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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How to cite this article: Dar MS, Shahid N, Waqas A, Baig YA, Khan AW. Dabrafenib plus Trametinib: a breakthrough in pediatric low-grade glioma therapy. *Health Sci Rep*. 2024;7:e1841. doi:10.1002/hsr2.1841