JPPT | Case Report

Myalgia and Rigidity as Adverse Effects of Trametinib Therapy

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Mitogen-activated extracellular kinase inhibitors, including trametinib and selumetinib, are increasingly used to treat pediatric low-grade gliomas. Trametinib, while administered orally and with minimal myelosuppression, is reported to cause rash, diarrhea, and fatigue. Selumetinib has been associated with skin irritation, diarrhea, and musculoskeletal pain. This case report describes an 8-month-old male with a low-grade glioma (LGG) that progressed 6 months post-chemotherapy and was started on trametinib due to its liquid formulation and minimal side effect profile. However, the patient developed severe diarrhea, abdominal pain, neck pain, rigidity, and decreased stamina. These symptoms necessitated discontinuation of trametinib, after which all symptoms resolved within a week. This case highlights the first reported instance of trametinib-induced myalgia and rigidity in a pediatric patient receiving trametinib therapy for a LGG. Clinicians should consider these rare but significant adverse effects when choosing an antineoplastic therapy for the treatment of progressive LGG.

ABBREVIATIONS MEK, mitogen-activated extracellular kinase; MRI, magnetic resonance imaging; LGG, low-grade glioma

KEYWORDS Gliomas; MEK inhibitor; myalgia; trametinib; case reports; side effects of drugs

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Information Box

What specific question does this report address?

Can trametinib have a side effect profile similar to other drugs in its class?

What does this report add to our current knowledge?

Trametinib therapy may cause myalgia and rigidity, which were previously only reported for salumetinib.

Introduction

Mitogen-activated extracellular kinase (MEK) inhibitors, such as trametinib and selumetinib, are being used with increasing frequency for the treatment of pediatric low-grade glioma (LGG).[1–4] MEK inhibitors stabilize the helical conformation of the MEK 1/2 activation segment, rendering it resistant to phosphorylation by rapidly accelerated fibrosarcoma (Raf), which arrests mitogen-activated protein kinase signaling.[5–7] Inhibition of this pathway causes cellular proliferation and cell cycle arrest.[8] The known benefits of MEK-inhibitor therapy include oral administration and minimal myelosuppression.[9–12]

Trametinib is associated with side effects, including rash, asthenia, diarrhea, fatigue, elevated creatine phosphokinase, and vomiting.[9,10] Selumetinib is reported to cause skin irritation, diarrhea, increased liver function tests, fatigue, increased creatine phosphokinase, arthralgia, and myalgias.[12–15] Indeed, up to 58% of patients on selumetinib experienced musculoskeletal pain, and 78% of patients exhibited elevated creatine phosphokinase levels. However, trametinib therapy in combination with dabrafenib has been reported to cause muscle pain.[16] Despite this, monotherapy of trametinib is not reported to have side effects, such as muscle pain or rigidity; however, the trial comparing trametinib monotherapy to trametinib and dabrafenib combination therapy only appeared to include adverse effects with an incidence of 30% or more.[2,16]

Case Report

In February 2022, a magnetic resonance imaging (MRI) of the brain was performed on an 8-month-old male weighing 6.6 Kgs (Figure 1) for evaluation of oral aversion, failure to thrive, and new-onset nystagmus. The MRI revealed a large, multilobulated, heterogeneously enhancing solid sellar/suprasellar mass with a significant mass effect on the midbrain, upper pons, and third ventricle. Subtotal tumor resection was performed, with pathology confirming the diagnosis of pilomyxoid astrocytoma with KIAA1549-BRAF fusion.

Figure 1. A photo of a patient before trametinib therapy.

After recovering from surgery, the patient was started on a 12-week induction course of carboplatin and vincristine. A follow-up MRI demonstrated a reduction in tumor size and enhancement, and he went on to complete a total of 8 maintenance chemotherapy cycles over the next 12 months. Treatment was well tolerated overall.

However, approximately 6 months after the completion of chemotherapy, a routine follow-up MRI demonstrated evidence of tumor progression. Based on this finding, the decision was made to start an oral MEK inhibitor. Specifically, trametinib was chosen because of its availability as a liquid formulation, and standard weight-based dosing was applied. Parents were counseled on common side effects, including skin rash, abdominal pain, diarrhea, fatigue, and cardiac dysfunction.

Clinical signs, laboratory values, and dosing of trametinib are presented in the Table. Five days after initiating therapy, the patient began having diarrhea and abdominal pain that necessitated a dose reduction. By week 2 of daily trametinib, the patient began experiencing neck pain, rigidity (Figure 2), postural changes, and decreased stamina. Laboratory evaluations at that time demonstrated normal blood calcium, liver enzymes,

Table. Clinical Signs, Lab Values, and Dosing of Trametinib

	Days After Initiation of Trametinib						
	0	**5**	**7**	**15**	**18**	**29**	**34**
Abdominal pain		†	†				
Diarrhea		†	†				
Fatigue				†			
Shoulder pain					†	†	
Neck pain/stiffness					†	†	
Trametinib dose (mg/day)	0.7	0.55	0.55	0.55	0.55	0*	
CK (U/L)					263	148	
Urine myoglobin					Negative		
Cr (mg/dL)			<0.20	0.22	0.24	0.34	
Na (mEq/L)			144	151	147	153	163
K (mEq/L)			4.3	3.9	3.7	4.4	
Cl (mEq/L)			113	117	113	116	
Ca (mg/dL)			9	9.3	9.4	9.5	
Mg (mg/dL)					1.8		
AST (U/L)					30		
ALT (U/L)					12		

ALT, alanine aminotransferase; AST, aspartate aminotransferase; Ca, serum calcium; Cl, serum chloride; CK, creatine kinase; Cr, serum creatinine; K, serum potassium; Mg, serum magnesium; Na, serum sodium

* Cessation of trametinib
† Presence of symptoms listed in first column

Figure 2. A photo of the painful, sustained neck rigidity on day 26 of trametinib therapy.

creatinine, and magnesium levels, as well as mild elevation of creatine kinase, and a negative urine myoglobin result. Supportive care measures, including massage, magnesium supplementation, and treatment with nonsteroidal anti-inflammatory drugs, did not help manage symptoms. Pain and rigidity worsened in intensity over the following week; he was unable to participate in play and physical/occupational therapy. Ultimately, his parents decided to discontinue trametinib on day 29 due to impaired quality of life. All musculoskeletal symptoms resolved within 1 week after discontinuation. The only additional medications the patient was receiving during this period were levothyroxine and desmopressin for hypothyroidism and diabetes insipidus, respectively. He had been on both medications without adverse effects for 2 years each before starting trametinib.

After discontinuing trametinib, the patient was restarted on a reduced dose of 0.175 mg of trametinib 2 months later. He is tolerating the lower dose, and dose escalation is being considered. If side effects recur, future treatment options include tovorafenib or monthly intravenous carboplatin.

Discussion

Gliomas are neuroepithelial tumors that originate from the supporting glial cells and are classified based on the type of cell involved, such as astrocytoma, ependymoma, or oligodendroglioma.[17] Cytological atypia, mitotic activity, anaplasia, microvascular proliferation, and necrosis are high-grade histological features, which are absent in LGG.[18] LGGs are typically slow-growing tumors.[17] However, more than 70% of LGGs gain higher-grade features or aggressive behavior within 10 years.[19] *IDH1*, *FUBP1*, *CIC*, BRAF, and *P53* gene mutations are all clinically associated with LGGs,[20–25] but radiation to the head is the only known environmental predisposing factor.[26]

Treatment of LGGs typically begins with a gross total resection, provided that more than 90% of the tumor can be resected, as this has been shown to have a significant impact on overall survival.[27,28] However, many tumors are not amenable to upfront resection, and medical therapies are therefore indicated. Carboplatin and vincristine are accepted as the standard of care for children with newly diagnosed LGG that are not amenable to surgical resection.[29,30] However, there is no standard of care for disease progression or recurrence. For this purpose, MEK inhibitors are being used; however, their superiority or inferiority to other treatments remains unclear.

Patients with LGGs have limited treatment options, and although the KIAA1549-BRAF fusion is of uncertain significance, those with BRAF V600 mutations tend to have a poor response to standard chemotherapy.[31,32] In this case, a MEK inhibitor was used to target possible increased mitogen-activated protein kinase signaling in the relapsed tumor, as well as for its formulation as a liquid. Selumetinib was considered but not chosen because it is only available as an oral capsule, which the child would have difficulty consuming. His parents were not advised as to possible muscle pain or rigidity with trametinib therapy, as these side effects had only been previously associated with selumetinib therapy.

Trametinib is a reversible, highly selective, allosteric inhibitor of MEK1 and MEK2.[2,5] All MEK inhibitors insert an aromatic group into a lipophilic site behind the inhibitor-binding pocket of MEK[5] to stabilize the helical conformation of the activation segment.[6,7] However, selumetinib contains a polar arm that forms hydrogen bonds with a bound nucleotide in MEK, while trametinib makes additional hydrophobic interactions along the activation segment helix and van der Waals contact with BRAF instead.[5] Although their interactions are different, similar mechanisms and structures likely contribute to the shared adverse effects of this class.

This case is the first that reports myalgia and rigidity as a clear time and dose related, unexpected adverse reaction attributed to trametinib monotherapy.[33] The Naranjo score is a method to assess whether there is a causal relationship between an identified untoward clinical event and a drug.[34] The Naranjo score in this clinical case was 6 (see Supplemental Table), corresponding to a probable association, as the adverse reaction followed drug administration, was a recognized response to the drug, was resolved by withdrawal from the drug, and could not be reasonably explained by other characteristics of the patient's clinical state.[35,36] This case report aimed to educate clinicians on these

potential side effects, so they can be considered when choosing between targeted therapies for LGGs. The authors recommend that trametinib be held when muscle pain and rigidity interfere with a child's activities of daily living and that the medication be resumed at a low dose when toxicities resolve. It is common for patients with unresectable LGG to require several second-line therapies, and trametinib should not be rejected as a treatment option if a lower dose proves to be efficacious and well tolerated.

Article Information

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