Thromboembolic toxicity observed with concurrent trametinib and lenalidomide therapy

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Abstract

The event-free survival of pediatric low-grade gliomas is poor, and patients often require multiple treatment strategies. While MEK and RAF inhibitors are efficacious in early-phase trials, not all patients respond and many experience progression following completion of therapy. Evaluating combination therapies that may enhance efficacy or prolong disease stabilization is warranted. We report our institutional experience using concurrent trametinib and lenalidomide in the treatment of primary pediatric central and peripheral nervous system tumors. Two of four patients using this combination therapy experienced severe thromboembolic events necessitating discontinuation of therapy. This combination requires further investigation, and we urge caution if used.

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Abbreviations:

CNS	Central nervous system
DVT	Deep vein thrombosis
EFS	Event-free survival
LVEF	Left ventricular ejection fraction
MAPK	Mitogen-activated protein kinase
MRI	Magnetic resonance imaging
OS	Overall survival
PD	Progressive diseases
PE	Pulmonary embolism
pLGG	Pediatric low-grade glioma
PNS	Peripheral nervous system
SD	Stable disease
STR	Subtotal resection

Abstract

The event-free survival of pediatric low-grade gliomas is poor, and patients often require multiple treatment strategies. While MEK and RAF inhibitors are efficacious in early-phase trials, not all patients respond and many experience progression following completion of therapy. Evaluating combination therapies that may enhance efficacy or prolong disease stabilization is warranted. We report our institutional experience using concurrent trametinib and lenalidomide in the treatment of primary pediatric central and peripheral nervous system tumors. Two of four patients using this combination therapy experienced severe thromboembolic events necessitating discontinuation of therapy. This combination requires further investigation, and we urge caution if used.

Introduction Pediatric low-grade gliomas (pLGGs) are the most common central nervous system (CNS) tumors in childhood.[1] Outcomes for pLGGs are generally excellent, with a 20-year overall survival (OS) between 85-96%.[2-4] However, event-free survival (EFS) is poor, with data from Children's Oncology Group A9952 demonstrating an EFS of 45% for all patients.[5] Patients consequently often require multiple treatment strategies.

Complete surgical resection is the mainstay of treatment, however, often is not feasible due to tumor location. Carboplatin-containing chemotherapy regimens are the standard upfront therapy for pLGGs, but there is no consensus on treatment following recurrence.[5-10]

The hallmark of pLGGs are genetic aberrations of the mitogen-activated protein kinase (MAPK) pathway, which lead to constitutive pathway activation.[11-14] MEK and RAF inhibitors target this pathway and are well tolerated and efficacious in reducing tumor size and improving EFS in phase 1 and 2 trials in patients with recurrent pLGGs.[15-19] However, not all patients respond to monotherapy, and many experience progression after completion of therapy. Thus, evaluating combination therapies that may enhance efficacy or prolong disease stabilization is warranted.

Lenalidomide is an immunomodulatory agent with CNS penetration that functions through anti-angiogenic,

anti-inflammatory, and pro-apoptotic effects, making it a promising candidate for the treatment of pediatric CNS tumors. Lenalidomide is well-tolerated in ongoing phase I trials for recurrent pediatric malignancies, with an anti-tumor effect demonstrated in recurrent pediatric CNS tumors.[20-22] Given their distinct mechanisms of action, concurrent MEK inhibitors and lenalidomide may present a rational combinatorial therapy. Further, both have available safety and dosing data in pediatric patients. Here we describe our institutional experience treating pediatric patients with a MEK inhibitor and lenalidomide concurrently, which to our knowledge has not been described.

Methods

A retrospective review of medical records of patients with primary CNS or peripheral nervous system (PNS) malignancies treated at Children's Hospital Colorado to identify children treated with MEK inhibitors and lenalidomide concurrently.

Results We identified four pediatric patients with primary CNS or PNS tumors treated with concurrent trametinib (0.032 mg/kg/day for patients less than 6 years old; 0.025 mg/kg/day for patients 6 years and older) and lenalidomide (25 mg/m^2/day on days 1-21 of each 28-day cycle).

Case 1

A 10-year-old boy had been diagnosed with an optic chiasm pilomyxoid astrocytoma (WHO grade II, BRAF:KIAA1549 fusion-positive). Prior therapy included subtotal resection (STR), carboplatin and vinblastine, focal photon radiation to 54 Gy, and trametinib. After three months of trametinib, he experienced progressive disease (PD) and started lenalidomide in addition to trametinib. Adverse effects on this combination were limited to grade 1 rash and paronychia. He achieved 15 months of stable disease (SD) on combination therapy before experiencing PD, prompting discontinuation of this therapy.

Case 2 A 6-year-old boy had been diagnosed with an optic pathway pilomyxoid astrocytoma (WHO grade II, BRAF:KIAA1549 fusion-positive). Prior therapy included carboplatin and vinblastine, everolimus, and two courses of trametinib.

At five years of age, six months into his second course of trametinib, he experienced PD and subsequently started lenalidomide in addition to trametinib. After three months of combination therapy, magnetic resonance imaging (MRI) of the brain demonstrated a partial response. Seven months into combination therapy, trametinib and lenalidomide were held due to urgent ventriculoperitoneal shunt revision. Within 48 hours, he experienced near-complete vision bilateral loss. MRI of the brain demonstrated a left posterior watershed territory hypoxic-ischemic injury (Figure 1), with stable appearance of the optic pathway mass. Multidisciplinary stroke team evaluation did not deem the area of injury plausibly attributable to direct surgical manipulation or tumor-associated vascular compression. Echocardiogram was negative for thrombus. He discontinued trametinib and lenalidomide and started radiation therapy.

Case 3 A 11-year-old girl was diagnosed with an optic pathway pilomyxoid astrocytoma (WHO grade II, BRAF:KIAA1549 fusion-positive). Prior therapy included carboplatin and vincristine, vinblastine monotherapy, carboplatin, vinblastine and cetuximab, and focal photon radiation to 54 Gy before starting trametinib. She received 15 months of trametinib with continued gradual PD before starting on lenalidomide. After four months of combination therapy, MRI of the brain demonstrated SD. However, surveillance echocardiogram identified severe biventricular dysfunction with a left ventricular ejection fraction (LVEF) of 18%, fractional shortening of 9%, and two mural thrombi in the left ventricular apex (Figure 2); the right ventricle was also moderately depressed. Echocardiograms performed prior to lenalidomide initiation demonstrated normal biventricular function. Trametinib and lenalidomide were discontinued, and she started enoxaparin and losartan. Within two weeks, the thrombi were no longer detectable by echocardiogram, and after two months, LVEF had recovered to 53%.

Case 4

A 15-year-old girl with neurofibromatosis type I received imatinib, STR, and trametinib to manage a

multiply-progressive plexiform neurofibroma (PN).

After 26 months of trametinib with continued gradual PD, lenalidomide was added to her therapy. She experienced SD for 12 months with no attributable adverse effects. The combination was held in preparation for resection of her PN. Given the safety concerns following the thromboembolic events described above, the decision was made to restart lenalidomide only.

Discussion

Recurrent pLGGs represent a therapeutic challenge. Exhaustion of evidence-based regimens may lead to off-study use of experimental therapies or combinations. Multiple studies support the use of MEK inhibitors and lenalidomide alone to treat pLGGs, but to date, there is no clinical trial evaluating this combination[15-19,21]. We describe four patients treated with concurrent trametinib and lenalidomide for multiply-progressive CNS or PNS tumors. Each patient had previously tolerated monotherapy with trametinib. However, two of four patients experienced significant thromboembolic events, requiring termination of this combination regimen.

Thromboembolic events have not been described in case reports or early-phase clinical trials of single-agent trametinib or lenalidomide in pediatric patients with CNS tumors.[17,20,21,23-27]The risk for thrombosis in adults treated with trametinib or lenalidomide monotherapy is also extremely low.[28-30]However, deep vein thrombosis (DVT) and pulmonary embolism (PE) were observed when trametinib was combined with the BRAF inhibitor, dabrafenib, for treatment of melanoma or non-small cell lung cancer.[31]

Similarly, immunomodulatory agents are associated with an increased risk for myocardial infarction, stroke, DVT, and PE in adults with multiple myeloma when used concomitantly with dexamethasone or chemotherapy.[32,34] The proposed mechanism for hypercoagulability is poorly understood but likely involves decreases in anticoagulant proteins and increases in platelet aggregation.[35] This may be potentiated by other prothrombotic agents, such as high-dose dexamethasone, as well as the direct action of immunomodulatory agents on endothelial cells previously damaged by chemotherapy.[32]

Cardiotoxicity has been associated with MEK and BRAF inhibitors and is thought to result from interference with the MAPK pathway, which may have a cardioprotective role.[31] Disruption of vascular endothelial growth factor signaling via downstream blockade of MEK leads to decreased nitric oxide production, thereby contributing to vasoconstriction, hypertension, and an imbalance between pro and anti-thrombotic factors. Angiogenesis, cellular apoptosis, and remodeling of myocytes may also rely on normal MAPK function.

This is the first report of trametinib used concomitantly with lenalidomide; thus, no pharmacodynamic data is available for the combination. Although the side effect profiles for each agent are unique, MEK inhibitor-induced cardiotoxicity combined with the prothrombotic properties of immunomodulatory agents may additively contribute to the risk for thrombosis in patients treated with trametinib and lenalidomide concurrently. Given the severe thromboembolic events experienced by these patients treated with concomitant trametinib and lenalidomide, this combination requires further investigation, and we urge caution if used concurrently.

Conflict of Interest Statement:

The authors declare no conflicts of interest.

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Figures

Figure 1:

A) Axial T2-weighted MRI demonstrates a solid and cystic optic pathway mass (black asterisk) in a 3-year-old boy

B) Axial diffusion-weighted MRI reveals restricted diffusion of the left posterior quadrant (white arrowheads) consistent with acute ischemia

C) 3D time-of-flight MR angiographic image at that time was normal

Figure 2: A) Apical 4-chamber view of echocardiogram demonstrates two apical, mural thrombi (white arrows); LA: left atrium, LV: left ventricle, RA: right atrium, RV: right ventricle

B) Parasternal short-axis view of echocardiogram demonstrates normal LV dimension with a small to moderate pericardial effusion (white dashed outline); RA: right atrium, RV: right ventricle