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ORIGINAL ARTICLE

Case series of dabrafenib-trametinib-induced pyrexia successfully treated with colchicine

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Abstract

The most common adverse event (AE) of dabrafenib and trametinib (DT) is pyrexia, which has been reported to occur in up to 71% of patients. Pyrexia resulted in therapy discontinuation in up to 26% of patients that otherwise were benefiting from the treatment. Little is known about the pathogenesis and optimal management of this common AE. We hypothesized that the etiology of pyrexia in patients treated with DT could be extrapolated from DT-related cutaneous adverse effects in which a paradoxical MAPK pathway activation has been identified. Based on preliminary data by our group suggesting an upregulation of the mitogen-activated protein kinases (MAPKs) in human lymphocytes exposed to dabrafenib and trametinib, specifically elevated expression of phosphorylated JNK (p-JNK), p38 MAPK (p-p38 MAPK), and ERK5 (p-ERK5), we hypothesized that the mechanism of MAPK pathway activation with DT therapy is similar to that reported in patients with familial Mediterranean fever (FMF), a rare, inherited condition characterized by episodes of fever and rash that responds exceedingly well to colchicine-based therapy in which the MAPK pathway is hyper-activated. Based on this association, our group explored the use of oral colchicine for the treatment of DT-associated pyrexia in five patients with metastatic melanoma.

Keywords Pyrexia · Dabrafenib · Trametinib · MAPK pathway · Colchicine

Introduction

The *B-RAF* gene is mutated in up to 50% of human malignant melanomas, and its protein product, B-RAF kinase, is a key part of the RAS-RAF-MEK-ERK (MAPK) pathway of cancer cell proliferation [1, 2]. Although properly selected patients with melanoma benefit from receiving B-RAF and/or MEK-targeted therapies, adverse events are common and can lead to therapy discontinuation [3]. The most common adverse event (AE) of dabrafenib and trametinib (DT) is pyrexia, which has been reported to occur in up to 71% of patients [4]. Pyrexia resulted in therapy discontinuation in 26% of patients that otherwise benefiting from the treatment [5].

The mechanism of DT-induced pyrexia is not well understood and little is known about the optimal management of this common AE. We hypothesized that the etiology of pyrexia in patients treated with DT could be related to the better-described mechanisms leading to DT-related cutaneous AEs. Skin toxicities commonly associated with DT, such as hyperkeratosis, keratoacanthomas and squamous-cell carcinomas, have been strongly associated with the paradoxical MAPK pathway activation in preclinical models and clinical studies [3]. Preliminary data from our group suggest that human lymphocytes incubated with dabrafenib and trametinib have elevated levels of mitogen-activated protein kinases (MAPKs), specifically elevated expression of phosphorylated JNK (p-JNK), p38 MAPK (p-p38 MAPK), and ERK5 (p-ERK5) have been identified. Interestingly, this mechanism of MAPK pathway activation is similar to that of patients with familial Mediterranean fever (FMF), a rare, inherited condition characterized by episodes of fever and rash that responds exceedingly well to colchicine-based therapy [6]. Based on this association, our group has used oral colchicine in five patients who developed DT-associated pyrexia [7]. Here, we report the results of this intervention.

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Case 1

A 69-year-old man diagnosed with B-RAF V600R mutated metastatic melanoma was initially treated with ipilimumab monotherapy and eventually the combination of ipilimumab and nivolumab due to disease progression. Unfortunately, the patient developed symptomatic therapy-related panhypopituitarism while on combination therapy. Hormone replacement was initiated, consisting of levothyroxine and hydrocortisone, the patient continued nivolumab; 4 months later, it was noted disease progression and targeted therapy with dabrafenib 150 mg twice a day in combination with trametinib 2 mg daily was initiated.

After 9 days of treatment with DT, the patient developed pyrexia of 39.6 °C. DT therapy was held, but the patient remained febrile with temperatures reaching 39.4 °C and accompanied by chills. Pyrexia did not improve despite the use of over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs). Two days after stopping DT, hydrocortisone 5 mg twice a day was started given the persistence of pyrexia; 2 days after discontinuation of DT, his pyrexia stopped; on the fourth day after discontinuation of DT, single-agent dabrafenib was reinitiated with a 50% dose reduction (75 mg twice a day); however, after 3 days of dabrafenib therapy in combination with hydrocortisone, the patient developed recurrent pyrexia with temperatures up to 38.8 °C again requiring holding of the dabrafenib. The patient was started on colchicine 1.2 mg oral daily followed by resolution of pyrexia. Two days later, dabrafenib was restarted with 50% reduction; 5 days later, dabrafenib was increased to full dose and trametinib 2 mg daily was added. A schematic representation of his treatment course is depicted in Table 1 and Fig. 3, which also shows similar data for subsequent patients.

After 24 days on treatment with full dose DT therapy and colchicine, the patient developed another episode of fever. DT was held for 2 days, while colchicine was continued, with resolution of pyrexia. The patient has remained on therapy with DT and colchicine for approximately 5 months. Unfortunately, complained of abdominal pain and was found to have hematobilia, after several interventions the patient died of septic shock secondary to hepatic abscesses. The only adverse event secondary to colchicine noted during this period was a grade 1 thrombocytopenia.

Case 2

This patient was a 52-year-old female diagnosed with B-RAF V600E mutated diffusely with metastatic melanoma. Due to the extensive tumor burden and elevated LDH

Table 1 Summary of cases prior and after treatment with colchicine

Case #	# Days of pyrexia prior colchicine	# Days DT was held prior colchicine	Dose reductions related to pyrexia prior colchicine (days)	# Days of pyrexia on colchicine	# Days DT was held on colchicine	Dose reductions related to pyrexia on colchicine (days held)	Medications used for pyrexia control prior colchicine	Colchicine dose
1	4	D (5) T (13)	D.50% reduction (8)	1	D (2) T (0)	(0)	Hydrocortisone 5 mg twice a day. Acetaminophen 650 mg PRN Ibuprofen PRN	1.2 mg bid
2	6	D (10) T (70)	D.50% reduction (60)	1	D (0) T (0)	(0)	Acetaminophen 1 g every 6 h Prednisone 20 mg daily	0.6 mg bid
3	2	D (3) T (3)	None (0)	0	D (0) T (0)	(0)	Acetaminophen 650 mg every 8 h. Prednisone 20 mg daily.	0.6 mg bid
4	8	D (11) T (11)	D.50% (28)	2	D (0) T (0)	(0)	Acetaminophen 650 mg PRN	1.2 mg bid
5	4	D (5) T (5)	D.50% reduction (4) T.50% reduction (4)	1	D (2) T (2)	(0)	Ibuprofen PRN	1.2 mg bid

*Patient unable to tolerate colchicine because of diarrhea

(4500 U/L), she was initiated on DT therapy (dabrafenib 150 mg twice a day and trametinib 2 mg daily). After 11 days of DT therapy, the patient experienced her first episode of pyrexia (39.8 °C). DT therapy was held and antipyretic management with acetaminophen 1 g every 6 h was started. She remained febrile for 3 subsequent days. After 7 days, dabrafenib, as a single agent, was reinitiated at a 50% dose reduction (75 mg twice a day) and trametinib was held. Four weeks later, the patient complained of arthralgia, panniculitis, and fevers ranging between 38.8–39.4 °C. Prednisone 20 mg daily was added with mild improvement of symptoms. An interval PET/CT showed a remarkable response to DT therapy.

Given the good response to dabrafenib therapy, but persistent pyrexia, prednisone and dabrafenib (75 mg twice a day) were continued for another 32 days when she developed recurrent pyrexia (38.6 °C) for 3 consecutive days. Dabrafenib was held and a subsequent PET-CT scan showed innumerable new FDG-avid metastasis in the axial and proximal appendicular skeleton.

After 2 months receiving dabrafenib at a 50% dose reduction and steroids without control of her fever, the decision was made to start colchicine 0.6 mg twice a day, so that potentially full dose therapy could be reinitiated. Three days after colchicine initiation, her pyrexia completely resolved. Dabrafenib and trametinib were reintroduced at full dose (150 mg twice a day/2 mg daily) and tolerated very well. The three drug regimen was continued for another 7 weeks with one single episode of pyrexia (39.4 °C) that resolved spontaneously. A subsequent PET/CT showed disease progression and chemotherapy was initiated.

Case 3

A 57-year-old male diagnosed with B-RAF V600E mutated metastatic melanoma was initially started on combination immunotherapy as part of a clinical trial (NCT02073123). Treatment was complicated by ICI-induced autoimmune gastritis and neuropathy, both managed with steroids. A follow-up PET/CT showed evidence of disease progression, forcing removal of the patient from the study and initiation of salvage therapy with dabrafenib 150 mg twice a day in combination with trametinib 2 mg daily.

Four months after initiation of DT therapy, the patient developed joint pain. Acetaminophen 650 mg every 8 h was started along with prednisone 20 mg daily. Four months after starting acetaminophen and prednisone, the patient developed pyrexia (39.4 °C) accompanied by chills and body aches for 2 consecutive days. DT therapy was held, prednisone 20 mg daily was continued and colchicine 0.6 mg twice a day was started. After holding DT and starting colchicine, the night sweats and chills resolved within 24 h, and the pyrexia resolved after 72 h. Dabrafenib (at a reduced dose of 150 mg bid and trametinib 2 mg daily were re-started and prednisone was increased to 40 mg daily for symptom management. The patient has been on the same therapy for 70 days and remains afebrile. His joint pain also resolved with colchicine initiation.

Case 4

A 41-year-old female was diagnosed with B-RAF V600E mutated metastatic melanoma involving the abdomen and brain. The patient underwent stereotactic radiosurgery to the left insular metastasis and was initiated on dabrafenib150 mg twice a day and trametinib 2 mg daily. Thirty-six days after starting with DT therapy, she developed pyrexia (39.6 °C), acetaminophen was started without improvement of symptoms and DT was held and resumed 4 days later without complications.

Forty days after DT initiation, PET/CT showed significant interval response to therapy and pembrolizumab was initiated, 11 days after triple therapy was initiated pyrexia (38.8 °C) recurred. Despite acetaminophen, pyrexia persisted and DT was held for 5 days; however, after complains of abdominal pain, the patient was admitted to the intensive care unit and diagnosed with autoimmune cholangitis related to immunotherapy. After 2 weeks of holding medications pembrolizumab in combination with DT was resumed, the patient had difficulty with pyrexia and night sweats, ultimately continued on dabrafenib at half dose with trametinib and pembrolizumab at full doses. She had an ongoing partial response to therapy. Five months later achieved complete remission of melanoma and DT was discontinued and continued pembrolizumab monotherapy.

Unfortunately, 2 months later, restaging imaging revealed new brain lesions and multiple subcutaneous metastases. DT therapy was reintroduced, 7 days after treatment initiation, the patient experienced pyrexia (39.5 °C), DT was held for 3 day and colchicine 1.2 mg twice a day was initiated. Nineteen days after colchicine and DT treatment the patient experienced temperatures ranging 37.2–38.5 °C. She developed diarrhea attributed to colchicine and was prescribed imodium. The colchicine dose was decreased to 0.6 mg twice a day with improvement of her diarrhea, the patient continue with DT and colchicine, she has remained afebrile for 90 days with complete response of the metastatic melanoma.

Case 5

A 57-year-old female diagnosed with metastatic melanoma harboring the B-RAF V600E mutation was started on pembrolizumab monotherapy. Unfortunately, after 2 months

of treatment, a PET/CT scan showed significant progression of disease. She was started on dabrafenib 150 mg twice a day in combination with trametinib 2 mg daily. Twenty days after DT initiation, the patient developed chills and a temperature of 39.4 °C. Ibuprofen was started with no improvement of pyrexia, DT was decreased by 50% for 4 days, but the patient remained febrile. DT was then held for 5 days and restarted at full dose in combination with colchicine 1.2 mg twice a day.

Seven days after resuming DT along with colchicine, the patient complained of intolerable episodes of diarrhea and pyrexia (39.9 °C). Colchicine was discontinued; acetaminophen and ibuprofen were initiated. On the following day, pyrexia was present again at 39.2 °C and DT was held. The patient was started on prednisone 20 mg for 7 days. After reintroduction of DT, pyrexia (37.6–38.9 °C) recurred. Dabrafenib was reduced by 50% and trametinib was held while prednisone was slowly tapered. A PET/CT showed near complete treatment response; however, DT was discontinued as the patient continued to experience pyrexia.

Discussion

Dabrafenib/trametinib was the first BRAF/MEK inhibitor combination therapy evaluated in clinical trials. Because of the significant improvement in survival, this combination therapy received accelerated FDA approval on November 2015 for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations [8]. Both drugs target the MAPK pathway: dabrafenib selectively inhibits mutant B-RAF protein that is constitutively activated, while trametinib selectively inhibits MEK1 and MEK2 proteins that are activated by RAF kinases (Fig. 1) [9].

Dabrafenib and trametinib are relatively well-tolerated drugs. Common grade 2 and grade 3 toxicities include pyrexia, skin events, gastrointestinal symptoms, arthralgia, fatigue, and headache [3]. Pyrexia, the most common AE of DT, has been reported to occur in 71% of patients treated with the recommended phase II dose of 150 mg twice-daily dabrafenib and 2 mg daily of trametinib [4]. Unfortunately, the presence of DT induced pyrexia results in drug discontinuation in up to 26% of patients [5]. The clinical features of pyrexia were described in detail by Menzies in 2015 [4], with a reported median time-to-onset of 19 days (range 1–82 days), and median duration of 9 days. The median time to onset for subsequent (2nd through 4th) events ranged from 24 to 31 days, and the median duration of subsequent events ranged from 4 to 5 days.

Little is known regarding the mechanism of DT-induced pyrexia or its optimal management [7]. A range of interventions have been described: dose interruption (46%), dose reduction (35%), antipyretics, (i.e., acetaminophen or NSAIDs) (18%), and steroids (13%). The various interventions (beyond treatment discontinuation) are variably effective. In patients who develop grade > 2 pyrexia, the median duration of dose interruptions was 11.5 days, potentially compromising the benefit of DT therapy [4, 7] (vemurafenib and cobimetinib, enrafenob and binimetinib).

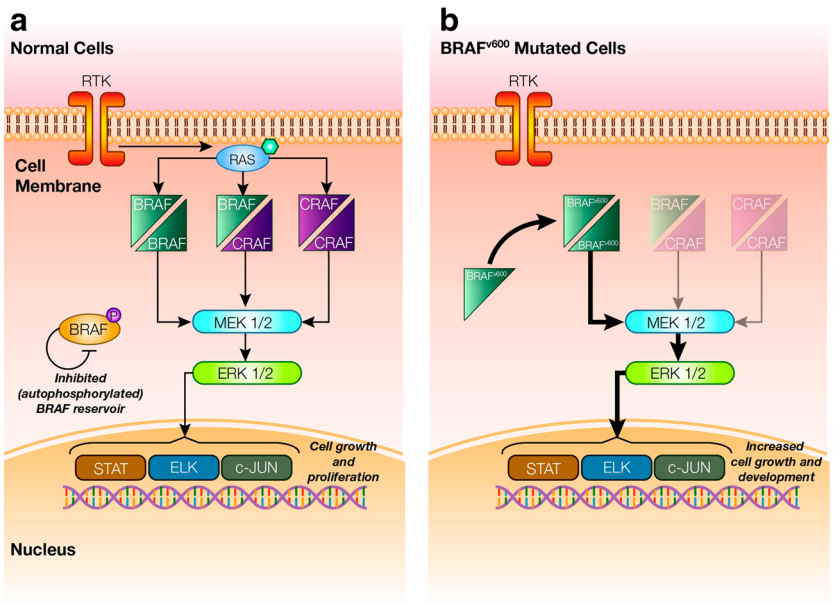

Fig. 1 MAPK pathway activation. (**a**).Under normal conditions, active BRAF signals through BRAF/MEK1/2 kinase activate ERK and its downstream effectors to regulate a wide range of biological activities including cell differentiation and proliferation. A reservoir of inhibited BRAF protein by an auto-phosphorylation mechanism is also present in the cytoplasm of normal cells. (**b**) In BRAF mutant cells, the gain of function mutation leads to stimulation of the MEK/ERK signaling in the absence of extracellular stimuli, allowing the cell to become self-sufficient in growth signals leading to tumor proliferation

It is worth to mention that AEs related to the combination of BRAF and MEK inhibitors differ among them; for instance, vemurafenib in combination with cobimetinib is most commonly associated in with rash, photosensitivity, serous retinopathy, alopecia, fatigue and liver enzyme elevation, interestingly the incidence of pyrexia is significantly less compared to darbafenib and trametinib [10]. We propose that these differences among side effects are related to the specific kinase suppressed by the MEK inhibitor, for example, cobimetinib is an inhibitor of mitogen-activated protein kinase 1 (MAP 2K1 or MEK1) while trametinib specifically binds to and inhibits MEK 1 and 2; a current study evaluating this differences is undergoing by our laboratory.

A possible mechanism to explain the pathogenesis of DT-induced pyrexia may be extrapolated from the mechanisms of toxicity of DT affecting the skin, and applied to cells of the immune system. Secondary skin changes, including hyperkeratosis, keratoacanthomas and squamous-cell carcinomas, gastric and colonic polyps, and recurrences of pre-existing malignancies have also been reported in patients receiving B-RAF inhibitors [3]. All of these conditions have been strongly associated with the paradoxical MAPK pathway activation in preclinical models and clinical studies [3]. The paradoxical MAPK signaling that occurs following B-RAF inhibition depends on the upstream activity of RAS, which can arise from either increased RTK signaling or directly as a result of activating mutations in RAS [3, 11, 12]. Based on these results, we hypothesized that pyrexia in patients treated with DT could be explained by the RAF inhibitor–dependent activation of MAPK signaling in B-RAF wild-type cells mediated by paradoxical MAPK-pathway activation in myeloid cells (Fig. 1) [7].

Our group identified clinical similarities of familial Mediterranean fever (FMF), a rare, inherited condition characterized by episodes of fever, joint pain and rash with the side effects associated with the combination of dabrafenib and trametinib. Although little is known about the MAPK–FMF interface, the pyrin protein has shown to be regulated in a MAPK p38-dependent mechanism in patients with FMF [7, 13]. (Figure 2) The potential ramifications of the crosstalk between NF-κB and MAPK signaling pathways are of immediate relevance to understanding the molecular pathogenesis of FMF and DT-associated pyrexia. The diagnosed of FMF warrants colchicine-based treatment. Based on this observation, our group used oral colchicine with success in patients who developed DT-associated pyrexia [7]. A recent published case report describing the development of NRAS-mutated chronic myelomonocytic leukemia shortly after the initiation of vemurafenib therapy in patients with metastatic B-RAF-mutant melanoma further supports our hypothesis. Peripheral blood mononuclear cells treated with vemurafenib demonstrated an elevated pERK:tERK ratio, as compared with the cells obtained while this patient was

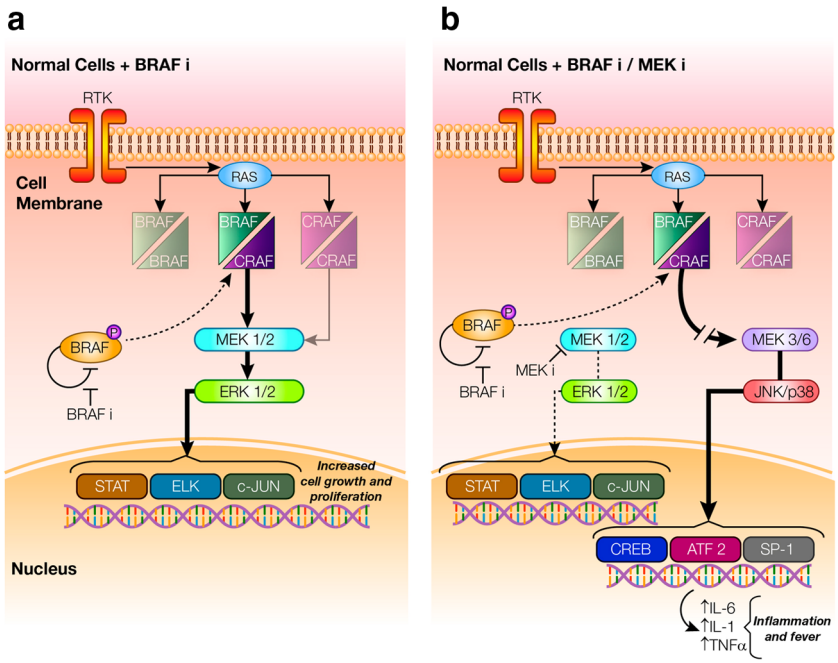

Fig. 2 Paradoxical MAPK pathway activation in wild-type and low activity BRAF. (**a**) The formation of RAF dimers occurs when cells with upstream RAS activity are treated with BRAF inhibitors. The BRAF inhibitor recruits BRAF protein from the cytoplasmic reservoir, where the binding of drug to one BRAF dimer induces the binding to and transactivation of its dimerization partner CRAF, a process that results in MAPK activation. (**b**) In the presence of BRAF and MEK inhibitors, we propose that the dimerization and activation of BRAF/CRAF dimer is shifted towards the activating of MEK 3/6 and then JNK/p38 leading to downstream DNA activation and increased production of IL-1, IL-6, and TNF-α, followed by inflammation and fever in a similar fashion to the pathogenesis of familial Mediterranean fever (FMF)

not taking the drug (1.25 vs. 0.98, $P = 0.02$), which is consistent with increased activation of ERK during treatment with B-RAF inhibitor [14].

Colchicine has been used in clinical practice for many years and is the gold standard treatment for FMF. The efficacy of colchicine in preventing acute episodes has been demonstrated in various randomized controlled studies [13]. It is thought to primarily concentrate in neutrophils and to inhibit their increased chemotactic activity during FMF attacks, although the precise mechanism by which colchicine exerts its effects in FMF is unknown [15, 16]. Colchicine is administered orally once the diagnosis of FMF is confirmed. Adult dosing is 1.2 to 2.4 mg/day. The standard formulation in the USA is 0.6-mg tablets; in Europe and Israel, the tablet strength is 0.5 mg [17]. Colchicine should be used at low doses and with caution in patients taking cytochrome P4503A4 inhibitor (i.e., cyclosporine, ketoconazole, ritonavir, clarithromycin, erythromycin, extended-release verapamil, extended-release diltiazem) because of the potential drug–drug interaction. In particular, individuals with renal impairment and patients on statins should stop these medications temporarily while taking colchicine [18]. Colchicine, despite its narrow therapeutic window, is a well-tolerated oral drug that is rapidly absorbed by the gastrointestinal tract [19].

Known colchicine toxicities include diarrhea, nausea, vomiting, gastrointestinal bleeding, thrombocytopenia, and liver and muscle toxicities. Colchicine might be considered in patients where dose interruptions, dose reductions,

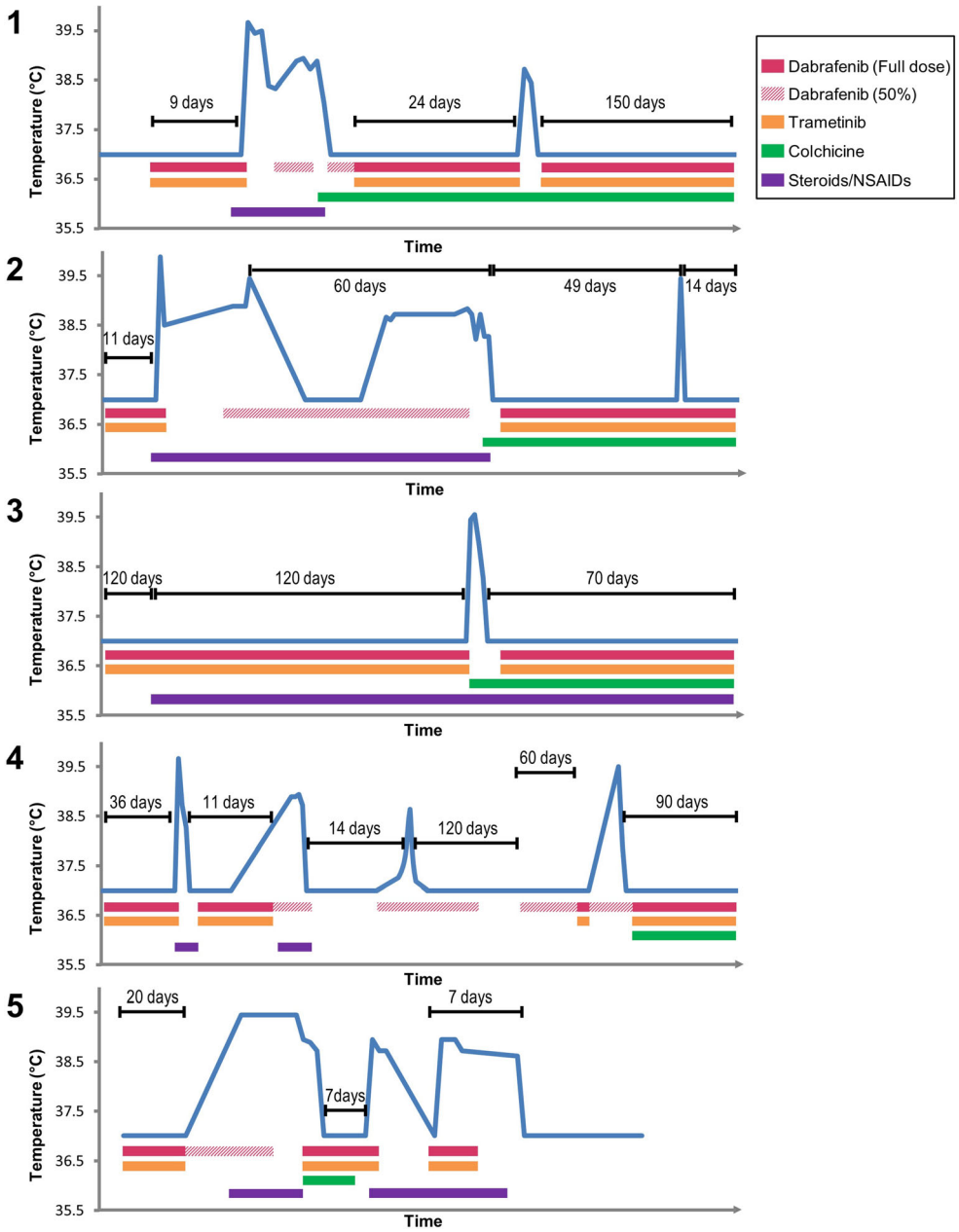

Fig. 3 Graphic summary of cases treated with colchicine

antipyretics, and corticosteroids have not been effective or are contraindicated (Table 1, Fig. 3).

In conclusion, the use of colchicine in the treatment of dabrafenib- and trametinib-associated pyrexia is a safe alternative to achieve patient compliance if pyrexia is present and other measures fail to control pyrexia. A clinical trial evaluating blood colchicine levels, MAPK pathway responses to colchicine and pyrexia response is currently underway in our group.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest, the authors have full control of the data; we agree to allow the journal to review their data if requested.

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