Characteristics of pyrexia in BRAF$^{V600E/K}$ metastatic melanoma patients treated with combined dabrafenib and trametinib in a phase I/II clinical trial


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Background: Pyrexia is a frequent adverse event with combined dabrafenib and trametinib therapy (CombiDT), but little is known of its clinical associations, etiology, or appropriate management.

Patients and methods: All patients on the BRF133220 phase I/II trial of CombiDT treated at the standard dose (150/2) were included for assessment of pyrexia ($n = 201$). BRAF and MEK inhibitor-naïve patients ($n = 117$) were included for efficacy analyses. Pyrexia was defined as temperature $\geq 38\, ^\circ C$ ($\geq 100.4\, ^\circ F$) or related symptoms.

Results: Fifty-nine percent of patients developed pyrexia during treatment, 24% of which had pyrexia symptoms without a recorded elevation in body temperature. Pyrexia was grade 2+ in 60% of pyrexia patients. Median time to onset of first pyrexia was 19 days, with a median duration of 9 days. Pyrexia patients had a median of two pyrexia events, but 21% had three or more events. Various pyrexia management approaches were conducted in this study. A trend was observed between dabrafenib and hydroxy-dabrafenib exposure and pyrexia. No baseline clinical characteristics predicted pyrexia, and pyrexia was not statistically significantly associated with treatment outcome.

Conclusions: Pyrexia is a frequent and recurrent toxicity with CombiDT treatment. No baseline features predict pyrexia, and it is not associated with clinical outcome. Dabrafenib and metabolite exposure may contribute to the etiology of pyrexia. The optimal secondary prophylaxis for pyrexia is best studied in a prospective trial.

Key words: melanoma, BRAF, dabrafenib, trametinib, pyrexia, fever

Introduction

For patients with advanced BRAF$^{V600E/K}$ melanoma, targeted therapy with the selective BRAF inhibitors vemurafenib or dabrafenib, or the MEK inhibitor trametinib, improve overall survival (OS) and progression-free survival (PFS) compared with chemotherapy [1–3]. Recently, treatment with combined dabrafenib and trametinib (CombiDT) has improved patient outcomes further. Randomized trials demonstrate a higher response rate and a longer PFS than dabrafenib monotherapy, longer OS than vemurafenib monotherapy, and less cutaneous toxicity [4–6]. The Food and Drug Administration approved CombiDT in early 2014. An adjuvant trial comparing CombiDT with placebo (NCT01682083) is ongoing. As opposed to the improvements in treatment efficacy and cutaneous toxicity observed with CombiDT over dabrafenib monotherapy, the incidence of pyrexia (temperature $>38.0\, ^\circ C$) is higher. Phase I–III trials of dabrafenib monotherapy reported pyrexia in 16%–26% of patients, and in Part C of the randomized phase II trial, pyrexia was reported in 26% on dabrafenib monotherapy [2, 5, 7–9]. In contrast, pyrexia occurred in the majority (39/55, 71%) of patients treated with CombiDT at the recommended phase II dose (RP2D) of 150 mg twice daily dabrafenib with 2 mg daily trametinib (150/2) in part C on the trial [4]. Fifty-eight percent (32/55) of patients on CombiDT in part C underwent dose reduction, the majority ($n = 19$; 59%) due to pyrexia [4], and 7% permanently discontinued treatment due to
toxicity, the most common reason being due to pyrexia (2/55, 4%) [10]. Initial reports from the phase III trial again demonstrate a higher incidence of pyrexia with CombiDT (51%) compared with dabrafenib monotherapy (28%) [5].

As yet, despite the high prevalence and morbidity of CombiDT-associated pyrexia, the clinical features, treatment outcome associations, etiology, and optimal management of this toxicity have not been examined in a large cohort of patients. Hence, this toxicity was investigated in all patients treated with CombiDT on the phase I/II trial (BRF133220) at the RP2D.

methods

patients and treatment

All patients treated with CombiDT 150/2 on the BRF133220 phase I/II trial (NCT01584648), in parts B (dose escalation), C (randomized phase II) and D (hydroxypropyl methylcellulose capsule), were included for post hoc analysis of pyrexia characteristics, predictors, and management (n = 201). This included patients who commenced on dabrafenib monotherapy and crossed-over to CombiDT at time of disease progression in part C, as well as those treated with 4 weeks of dabrafenib monotherapy who then transitioned to CombiDT as planned cross-over in part D. One patient was excluded due to a likely erroneous recorded treatment with prednisone at dose of 250 mg daily. The study was carried out with ethics committee approval.

baseline patient and disease assessments

Characteristics of patients at the time of commencing treatment with CombiDT were examined including age, sex, BRAF genotype, Eastern Cooperative Oncology Group (ECOG) performance status (PS), lactate dehydrogenase (LDH), American Joint Cancer Committee Metastasis (M) stage [11], and RECIST sum of diameters (SoD) at baseline [12]. Details of prior treatments for metastatic disease, including chemotherapy and immunotherapy, were also assessed. Baseline hematology and biochemistry was assessed.

definition of pyrexia

Adverse events (AE) preferred terms entered into the clinical trial database including: pyrexia (≥38.5°C, ≥100.4°F), chills, night sweats, influenza-like illness, hypotension, cytokine release syndrome, and systemic inflammatory response syndrome were all considered pyrexia.

assessment of pyrexia

Each event of pyrexia was analyzed for CTCAE v4.0 grade, timing of onset from start date of treatment or resolution of the previous event of pyrexia, duration, and the presence of concomitant symptoms. The total number of pyrexia events per patient was noted, and each event was analyzed separately. A pyrexia event was considered to have resolved if complete end dates were entered into the clinical trial database for all related AEs terms, and a subsequent event commenced if a new AE term was entered at a later date. The grading of a pyrexia event was determined by the highest CTCAE grade for any of the terms included in the pyrexia definition.

management of pyrexia

Initial protocol guidelines [4] required that for pyrexia with a temperature ≥38.5°C or a complication (any temperature with associated rigors, chills, dehydration, hypotension, dizziness, or weakness), dabrafenib was to be held and trametinib continued until resolution of pyrexia, then dabrafenib was to be restarted at a lower dose. For less severe pyrexia (temperature <38.5°C with no associated symptoms), dabrafenib was to be withheld until resolution of pyrexia, with recommencement at the same dose with acetaminophen (APAP) or nonsteroidal anti-inflammatory (NSAID) cover for 2–3 days. Dabrafenib could also be dose-reduced per investigator discretion. As the trial progressed, oral corticosteroids were permitted as per investigator discretion.

Initiation of APAP, NSAIDs, or corticosteroids in patients with pyrexia while on trial were considered to be for the use of acute management or secondary prophylaxis of pyrexia, and were classified as an antipyretic (APAP, NSAIDs) or corticosteroid. These, along with dose interruptions and reductions, were defined as pyrexia management measures. Only measures with complete data including start and end dates were included. Measures that commenced at onset of a pyrexia event and ceased at time of pyrexia resolution were considered acute management. Measures started during an event or within 21 days of the event end date and continued for at least 30 days after the event end date while on CombiDT were considered secondary prophylaxis. This definition ensured that patients remained on CombiDT and on a prophylaxis measure for a sufficient time period to remain at risk for further pyrexia, such that the relative efficacy of prophylaxis could be examined.

pharmacokinetic analyses

The relationship between the fraction of patients having pyrexia and exposure was explored graphically by combining safety data into terciles or quartiles of exposure [predicted average concentration (\(C_{avg}\)) or predose concentration (\(C_{pred}\))] in patients from part C who received CombiDT 150/2, as well as those who received 150/0 and 150/1 doses (\(n = 124–161\)). The association of pyrexia incidence and trametinib exposure (\(C_{max}\)), dabrafenib exposure (\(C_{max}\), \(C_{min}\)), and exposure to the active metabolites hydroxy- and desmethyldabrafenib (\(C_{min}\)) was examined. Data were limited to patients with onset of pyrexia within the first 4 months of dosing, as PK draws were carried out only during the first several cycles of treatment. Evaluations of the relationship between exposure and pyrexia were not carried out on the patients treated in part D due to the small sample size.

statistical analysis

The data cutoff for each part were: part B, 25 May 2012; part C, 31 May 2012; and part D, 25 September 2012. Only AEs with complete start and end dates were included in this analysis. In the case of multiple adverse events in the definition of pyrexia occurring simultaneously, the duration of the pyrexia event was calculated as the number of days from the start date of the first event to the end date of the last event. Post hoc efficacy analyses were carried out only in patients who were BRAF or MEK inhibitor naive (\(n = 117\)), as the efficacy of CombiDT after prior BRAF inhibitor is poor [13]. At the data-cut for this manuscript, OS data for the trial were not yet mature and were not examined.

Standard descriptive statistics were used to summarize distributions. Analyses investigating the association between baseline patient and disease characteristics and pyrexia occurrence (yes or no) were carried out using logistic regression. Overall response rate (ORR), change in tumor measurements by RECIST, and PFS were analyzed by pyrexia occurrence and grade (0, 1, 2, and 3+). ORR was estimated and reported with 95% confidence intervals (CIs). Kaplan–Meier estimates were calculated for PFS. Cox proportional hazards model analysis was used to investigate the relationship between the occurrence of pyrexia (yes or no) and PFS using a time-dependent formulation for pyrexia. The same patient and disease characteristics used in the logistic regression analyses were explored in the Cox modeling.

results

clinical features of pyrexia

Pyrexia was reported in 119 of 201 (59%) patients. Of these patients, 28 (24%) had symptoms of chills, night sweats, influenza-like illness, hypotension, cytokine release syndrome, and/or systemic inflammatory response syndrome recorded without a documented increase in body temperature (≥38°C)
(supplementary Figure S1, available at Annals of Oncology online). Among patients with pyrexia, 58/119 (49%) had only 1 event, 20 (17%) had 2 events, 16 (13%) had 3 events, and 25 (21%) had 4+ events (median 2, maximum 15 events).

The median time to onset of first pyrexia event from start of treatment was 19 days (range 1–82 days), with a median duration of 9 days (Figure 1). 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. First event was grade 1 in 66 of 119 (55%) patients, grade 2 in 46 (39%) patients, and grade 3+ pyrexia occurred in only 7 (6%) patients. Subsequent events had a similar severity profile, and the maximum grade of pyrexia observed for each patient during any pyrexia event was grade 1 in 39%, grade 2 in 50%, and grade 3+ in 10% of patients.

Rash occurred in 42/119 (35%) of patients during first pyrexia, commencing after pyrexia onset in 34/42 (81%). During pyrexia, median creatinine clearance remained similar to pretreatment levels, and median neutrophil count remained in the normal range.

**management of pyrexia**

Several management strategies were used, often in combination. For first pyrexia, 43% of patients received no specific pyrexia management, 46% underwent dose interruption, 35% dose reduction, 18% antipyretics, and 13% corticosteroids (supplementary Table S1, available at Annals of Oncology online). For subsequent events, the proportions of management strategies remained similar. In the first three events (n = 221), management differed by pyrexia grade. For grade 1 versus grade 2+ pyrexia, 63% versus 24% patients received no specific management, respectively, while dose interruption (26% versus 66%), dose reduction (17% versus 44%), corticosteroids (6% versus 20%), and antipyretics (9% versus 23%) were used more frequently in those with grade 2+ pyrexia. Dose interruptions for grade 1 pyrexia lasted a median 4 days, while interruptions for grade 2+ pyrexia lasted a median of 11.5 days.

It was not possible to determine the relative success of any specific prophylaxis strategy in preventing subsequent pyrexia because of the use of several management strategies concurrently (e.g. dose reduction and corticosteroids), the unbalanced numbers of specific management strategies adopted, and the small number of patients meeting the prophylaxis definition used in this analysis. However, in patients who received no specific pyrexia management, 57% (29/51) had no further pyrexia after the first event, and 67% (20/30) had no further pyrexia after the second event. Three patients (1%) permanently discontinued treatment due to pyrexia.

**pharmacokinetic analysis**

A trend toward an increased proportion of patients experiencing pyrexia with increased dabrafenib \( C_{avg} \) and hydroxy-dabrafenib \( C_{min} \) was observed (Figure 2 and supplementary Figure S2, available at Annals of Oncology online). There was no observed

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Figure 1. Timing and grade of events of pyrexia.
association between pyrexia and trametinib $C_{\text{min}}$, or desmethyl-dabrafenib $C_{\text{min}}$.

**baseline patient characteristics and pyrexia development**

There was no association between any baseline patient or disease characteristic and pyrexia (supplementary Table S2, available at *Annals of Oncology* online). A trend toward a higher rate of pyrexia in patients with $BRAF^{V600K}$ melanoma, M1c stage, and in middle age (40–64 years) was observed, but these factors did not reach statistical significance (all $P > 0.05$). Other baseline characteristics of sex, LDH, baseline tumor burden, ECOG PS, and previous history of brain metastasis did not show an association with pyrexia incidence. There was no difference in renal function at baseline in those who developed pyrexia than those who did not. Similarly, there was no association of baseline renal function and pyrexia by grade of first pyrexia event (nil, grade 1, 2, and 3+).

**patient outcomes and pyrexia**

Efficacy analysis carried out in 117 BRAF and MEK inhibitor-naive patients, 82 with pyrexia and 35 without, showed no statistically significant associations between pyrexia and the maximum reduction in SoD of baseline target lesions, the ORR, or PFS (Table 1, Figure 3A). Similarly, there was no association

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*Figure 2. Relationship between dabrafenib, metabolites (150/2 cohort), and trametinib (all cohorts) pharmacokinetics and pyrexia.*
Table 1. Response to CombiDT and pyrexia occurrence in BRAF and MEK inhibitor-naïve patients (N = 117)

<table>
<thead>
<tr>
<th></th>
<th>Patients with pyrexia (N = 82)</th>
<th>Patients without pyrexia (N = 35)</th>
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<tbody>
<tr>
<td>Median maximum change from baseline in the sum of target lesion diameters, % (range)</td>
<td>–66 (–100.0 to 0.0)</td>
<td>–47.5 (–100.0 to 15.0)</td>
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<tr>
<td>Best confirmed response</td>
<td>n</td>
<td>%</td>
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<tr>
<td>CR</td>
<td>8</td>
<td>10</td>
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<td>PR</td>
<td>52</td>
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<td>SD</td>
<td>21</td>
<td>26</td>
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<tr>
<td>CR + PR</td>
<td>60</td>
<td>73 (95% CI 62.2–82.4)</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>9.3 (95% CI 8.6–13.2)</td>
<td>10.1 (95% CI 5.4–NR)</td>
</tr>
</tbody>
</table>

CI, confidence interval; CR, complete response; NR, not reached; PFS, progression-free survival; PR, partial response; SD, stable disease.

Figure 3. PFS in BRAF and MEK inhibitor-naïve patients by (A) pyrexia (yes/no), and (B) grade (n = 117).
with PFS and pyrexia by maximum grade over all pyrexia events (nil, grade 1, 2+) (Figure 3B).

**discussion**

The combination of dabrafenib and trametinib has recently been approved by regulatory agencies in patients with advanced BRAFV600E/K-mutant melanoma, both in the United States and Australia. Although pyrexia is the most common toxicity observed with this regimen, little is known about its features and management. In this analysis of patients on phases B–D on the phase I/II trial treated at the recommended CombiDT dose (150/2), we demonstrate that pyrexia is frequent and recurrent, can manifest as febrile-like symptoms in the absence of a documented body temperature elevation, and is not associated with baseline patient characteristics such as renal function, disease burden or PS.

The inclusion of all patients treated on the phase I/II trial at the now standard dose of CombiDT, the detailed and prospectively collected clinical dataset, and the inclusive definition of pyrexia, provided a large analytic sample. Nevertheless, data were reliant on self-reporting of symptoms by patients and accurate collection and entry of data into the clinical trial database by site investigators and staff, and the assumption that any concomitant antipyretic medications or dose reductions in patients with pyrexia were for the purpose of acute pyrexia management and/or prophylaxis may have biased the study results.

This study confirms that pyrexia is a common adverse event with CombiDT. Usually occurring within the first 3 weeks after initiation of treatment, pyrexia is episodic and often resolves with antipyretics or dose interruption. About half of patients who develop pyrexia have recurrent events, and most have at least one grade 2+ pyrexia event (i.e. temperature >39.0°C). Interestingly, a quarter of patients with pyrexia have chills, hypotension, and rigors without a recorded body temperature elevation, suggesting that the pyrexia process may be under-reported in clinical trials conducted to date. Age, gender, renal function, BRAF genotype, ECOG PS, and disease burden did not identify patients at greater risk of pyrexia.

The addition of the MEK inhibitor trametinib to dabrafenib reduces dabrafenib-induced hyperkeratosis and cutaneous squamous-cell carcinoma by counteracting the paradoxical activation of wild-type BRAF in keratinocytes [14, 15]. Similarly, unopposed MEK inhibition with trametinib results in acniform rash in 19% of patients [3], and the addition of dabrafenib reduces this (8%) [5]. In this study, rash developed in a minority of patients, usually after pyrexia onset, possibly due to unopposed trametinib action on the skin as a result of withholding dabrafenib while continuing trametinib (as suggested in the initial study protocol), or withholding both drugs together where trametinib has a significantly longer half-life [7, 16].

The etiology of pyrexia in patients treated with CombiDT is currently unclear; pyrexia also occurs to a lesser extent with other BRAF inhibitors and BRAF/MEK inhibitor combinations [1, 17, 18]. Its relationship with MAPK inhibition is unknown, but within the context of the patient numbers analyzed here, pyrexia was not statistically significantly associated with RECIST responses or PFS although patients with pyrexia had numerically higher response rates. A correlation with pyrexia was observed with both average dabrafenib concentration and hydroxy-dabrafenib Cmin levels in the study cohort dosed at 150/2 as well as in dabrafenib monotherapy patients; however, no association was seen with other dabrafenib metabolites or trametinib. The increased incidence of pyrexia with CombiDT compared with dabrafenib monotherapy, and the lack of pyrexia with trametinib monotherapy [3, 16], suggests that trametinib influences the dabrafenib-driven pyrexia process, but the exact nature of this is still unknown and requires further research. Furthermore, the episodic nature of pyrexia versus the rather steady exposure levels of the parent drugs and metabolites suggest that exposure is likely not directly related, but rather may set the stage for other factors to induce pyrexia [19].

A detailed assessment of the relative efficacy of acute and secondary prophylaxis pyrexia management measures was not possible in this retrospective study. The clinical trial was not designed to describe or evaluate the effectiveness of management strategies, some data were incomplete due to a lack of start and end dates for management measures and end dates for pyrexia resolution, and prophylaxis was not used in a consistent manner. A single-center study has indicated that corticosteroids (e.g. prednisone 20–25 mg) are effective prophylaxis for recurrent pyrexia, may preclude dose reduction, and may allow for dose re-escalation in selected patients [20].

Based on our experience, effective management of pyrexia involves prompt interruption of both dabrafenib and trametinib at the very first symptom of pyrexia or its associated prodrome. This is best achieved with effective patient education and ongoing communication with the treating team. Early intervention results in prompt resolution of events, usually within 24 h of dose interruption. Acetaminophen and NSAIDs may alleviate symptoms during pyrexia. We do not routinely recommend a septic work-up for patients with uncomplicated pyrexia and without localizing infective symptoms. Recommencement of CombiDT can safely occur 24 h after pyrexia resolution. In cases of recurrent or severe pyrexia, an intermittent dosing regimen, and/or corticosteroids may be useful. Unlike other toxicities such as fatigue, dose reduction does not appear to reduce the risk of pyrexia recurrence and is best avoided. In many cases, pyrexia does not recur; however, rarely events may recur several months later, and patients and clinicians must remain alert to recognize and manage pyrexia at any time on treatment.

The results of this retrospective study suggest that CombiDT-associated pyrexia is a prevalent and recurrent toxicity with no clinical associations. A prospective study specifically examining pyrexia, exploring potential central and peripheral etiologies as well as secondary prophylaxis strategies, are required to examine this toxicity further. The current phase III trials may also assist with our understanding of this process, although they were not specifically designed to explore pyrexia. In the meantime, the management algorithm above offers guidance for clinicians using this regimen.

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disclosure

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