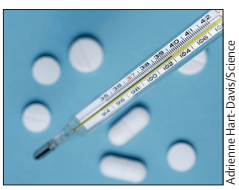
Shedding light on dabrafenib-induced fevers in patients with melanoma



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The introduction of drugs that target the *BRAF*^{V600} mutation in the MEK signalling pathway in melanoma ushered in a new era in the treatment of patients with melanoma. Vemurafenib was the first of the BRAF inhibitors to be introduced, followed by dabrafenib, and then encorafenib. The efficacy of these inhibitors was increased by the addition of MEK inhibitors (eg, trametinib) that act downstream of mutant BRAF. Many side-effects are common to all three BRAF inhibitors, such as fatigue, anorexia, muscle pain, constipation, hair loss, and skin side-effects (eg, actinic keratosis, hyperkeratosis, pruritus, and photosensitivity).[1] Dabrafenib has an additional side-effect of pyrexia, which was recorded in 16–26% of patients treated with dabrafenib alone and 50–71% of patients treated with dabrafenib plus trametinib.[2,3] These proportions of patients with pyrexia were much higher than those recorded for combinations with encorafenib plus binimetinib (1·7%) and vemurafenib alone (5%) in the COLUMBUS study.[4] The clinical characteristics of pyrexia associated with dabrafenib plus trametinib include fever of 38°C or higher, chills, rigors, night sweats, or flu-like symptoms.[3,5] Patients treated with the combination had a median of two events and 21% had four or more events. The median time to onset from the start of treatment was 19 days and the median duration was 9 days.[5] If untreated, pyrexia has the potential to worsen and can result in hypotension from dehydration.

The cause of pyrexia has attracted much attention but is largely unknown. One study including five patients treated with dabrafenib and trametinib suggested that fevers were due to paradoxical elevation of MAP kinases.[2] Pyrexia was not associated with common genetic variation or HLA polymorphisms. Blood marker tests in 15 patients treated with dabrafenib and trametinib revealed a correlation with elevated neutrophil count and C-reactive protein concentrations in 11 patients who developed fever.[6] The cytokine profiles of 34 patients being treated with the combination of dabrafenib plus trametinib revealed an increase in IL1-β and IL6 concentrations in the first week of treatment.[7] The study found no relation to concentrations of dabrafenib, its metabolites, or trametinib. The correlation with IL1-β concentrations were of particular interest because previous studies in mice identified this cytokine as the main mediator of pyrexia.[8]

A study by Hajek and colleagues[9] provides insights into the pathophysiology of dabrafenib-related fevers that might improve understanding of the changes in blood referred to in these studies and lead to changes in the management of pyrexia. The authors reported that dabrafenib, but not vemurafenib, activated murine splenic and bone marrow-derived dendritic cells and increased the production of IL1-β. The addition of trametinib to dabrafenib further increased activation of the dendritic cells and IL1-β production but reduced production of tumour necrosis factor, IL12, and IL23. Both drugs were found to activate NOD-like receptor (NLR) C4 inflammasomes in the dendritic cells, as shown by activation of caspase-1 and cleavage of pro-IL1-β to IL1-β. Dabrafenib, but not vemurafenib, was also found to increase IL1-beta concentrations in primary human dendritic cells and unstimulated human monocytes. The structure of dabrafenib and other BRAF inhibitors is well described, and therefore key differences between the molecules that are being recognised by inflammasomes might be revealed by further study.

Inflammasomes are large multiprotein complexes in the cytosol that have receptors that bind pathogen-associated molecular patterns or cell damage-associated patterns. Inflammasomes form a complex with adaptor proteins such as apoptosis-associated speck-like protein which can bind and activate caspase-1. Once activated, caspase-1 can cleave pro-IL1-β and pro-IL18 to their active forms. Caspase-1 also activates gasdermin-D, which forms oligomers in the cell membrane that allows the release of IL1-β and IL18. The cell swells and ruptures, undergoing a form of cell death called pyroptosis. The inflammasome receptors can be grouped into the NLR pyrin domain family and absent in melanoma receptors. NLRP3 is the best studied inflammasome receptor and can be activated by several stimuli. Dabrafenib appeared to activate NLRC4 inflammasomes[9] but further characterisation of the inflammasomes involved is needed since the inhibitors used to characterise NLRC4 might also inhibit the NLRP3 inflammasome.

One of the features of dabrafenib-induced pyrexia is that most patients eventually tolerate the treatment quite well, which raises the question as to the adaptive mechanism involved. Again, the inflammasome hypothesis offers an explanation in that inflammasome receptors are subject to ubiquitination and degradation by autophagy. Further support for their involvement in pyrexia might be obtained by successful treatment of patients with blocking antibodies against IL1-β, such as canakinumab. Canakinumab is usually given subcutaneously every 4 weeks, and a single injection might even be considered for prophylactic administration. Specific inhibitors of NLRP3, such as MCC950 and CY-09,[10] also exist, but whether or not dabrafenib interacts with the NLRP3 receptor remains under investigation. NLRP3 inhibitors would have utility in establishing the pathogenesis of the fevers and lead to further assessment of their use relative to the existing treatment of pyrexia with corticosteroids. New approaches to managing this distressing side-effect will be particularly important as this drug combination transitions into the adjuvant setting.

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Multiplicity in oncology randomised controlled trials: a threat to medical evidence?

Randomised controlled trials offer several advantages over observational studies in establishing whether cancer treatments improve patient outcomes. First, randomised controlled trials minimise bias and confounding. Observational studies judge treatments that were chosen not at random but deliberately by physicians, and the decision to treat or not treat an individual might be affected by patient characteristics, a type of bias called confounding by indication. Randomised controlled trials prescribe therapy and avoid this limitation. Second, randomised controlled trials restrict multiple hypothesis testing. Randomised controlled trials typically address a specific research question with a prespecified primary outcome and a predefined statistical analysis plan. This approach reduces the ability of investigators to assess multiple outcomes, which in turn minimises the risk of a spurious (eg, false positive) finding. For these reasons, David Sackett placed randomised controlled trials at the apex of the hierarchy of evidence.[1] Yet in the past 10 years, one of these assumptions is increasingly being questioned. Randomised controlled trials have proliferated in number, often test similar compounds with similar molecular targets, and are often run in redundant and duplicative trial portfolios or agendas. For this reason, multiplicity has emerged as a new threat to the validity of conclusions drawn from randomised controlled trials. In this Comment, we explore this issue.

Multiplicity, or the number of times an analysis can be run, has long been recognised as a threat to causal inference from observational studies. Patel and colleagues[2] found that if researchers are afforded