



## Chakalaka-induced vasodilatation in patients with chronic myeloid leukaemia on tyrosine kinase inhibitors

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The tyrosine kinase inhibitors (TKIs) are a new group of drugs providing targeted therapy for chronic myeloid leukaemia (CML). They vastly increase survival, but compliance is an issue because they cause vasodilatation as a side-effect. In our experience spices, especially the African sauce or relish chakalaka (that contains garlic and chilli), may aggravate the vasodilatation induced by TKIs. These spices produce serious oedema and headaches. We have found that stopping the intake of spice allows some patients to maintain therapeutic doses of TKIs. This has been confirmed and put into practice by a growing number of South African haematologists. As spice that contains chilli and garlic is used by a large proportion of our South African (and the world) population, this observation is significant in that it can help to prevent the 'compliance decay' associated with TKI therapy, which adversely affects patient survival.

CML represents up to 20% of all leukaemias, with a worldwide incidence of about 1 - 2/100 000 per year. There may be up to 450 new cases annually in South Africa. Imatinib is a tyrosine kinase receptor antagonist that inhibits the mutated tyrosine kinases such as Bcr-Abl, c-kit, and platelet-derived growth factor receptor (PDGFR) in some malignancies. It has revolutionised the treatment of Philadelphia chromosome-positive CML.

Imatinib causes fluid retention in 7 - 81% of patients.<sup>1</sup> Facial, peri-orbital and peripheral oedema occur most frequently. It causes headache in 27 - 39% of cases,<sup>1</sup> and even cerebral oedema.<sup>2</sup> Pietras *et al.*<sup>3</sup> have proposed that a second, still elusive, trigger is needed for these rare effects to occur. Dasatinib, another TKI, is a potent PDGFR inhibitor that causes fluid retention in up to 50% of patients.<sup>4</sup>

Compliance with imatinib is vital to prevent relapse, so factors that may cause adverse reactions and diminish compliance need to be excluded. We report 4 cases of chronic-

phase CML treated with TKIs, in which worsening adverse reactions were associated with the use of chillies and garlic.

### Case reports

A 36-year-old man had quickly achieved complete haematological remission of CML on imatinib 400 mg/d. Three months later he developed severe headache and pedal oedema hours after eating tinned chakalaka. Apart from very mild mitral incompetence controlled with diuretics, there was no other likely cause for the oedema. The oedema subsided, but was still present when we saw him 2 days later. It disappeared within 4 days, without adjustment of the imatinib dose. After this he avoided chakalaka and spices, and the oedema did not recur.

Subsequently, 3 more patients on TKIs experienced adverse reactions probably related to consuming garlic and chillies, two main ingredients of chakalaka.

The second patient was a 70-year-old man with Philadelphia chromosome-positive CML. He had hypertension, which was controlled well with nifedipine and perindopril. Three weeks after starting imatinib 400 mg/d he developed oedema, rash and headaches. He continued at the same dose, but after several months had not achieved haematological remission. The imatinib dose was increased to 600 mg/d, and the headaches intensified. There were no abnormal neurological findings. The symptoms subsided within 10 days after he avoided chillies and garlic. He later achieved a complete cytogenetic remission without further adverse effects.

The third patient was a 20-year-old woman with Philadelphia chromosome-positive CML who could not tolerate imatinib 400 mg daily because of intractable oedema, headaches, and nausea. She took no other medication and was normotensive. Because of the adverse effects and progressive disease, she was switched to dasatinib 140 mg daily. The oedema and nausea disappeared, but she immediately developed incapacitating headaches, without hypertension or neurological signs. These disappeared within 10 days after she avoided chillies and garlic, without adjusting the dasatinib dose. After she ate a spicy meal a few weeks later the headaches recurred briefly. Unfortunately, after 4 months she had not achieved an adequate response and was prepared for a stem cell transplant.

The fourth patient was a 28-year-old man with Philadelphia chromosome-positive CML who was started on dasatinib 100 mg daily. He developed a swollen leg and a severe headache 12 hours after eating food spiced with a lot of curry powder that contained chillies. The symptoms had all but disappeared

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by the time we saw him 60 hours after the meal. He refused to have a deep-vein thrombosis excluded. His recurrent headaches improved when he avoided spices. He was found to have the *CYP3A4\*1G* allele, single-nucleotide polymorphism, of the *CYP3A4* variant of P450,<sup>5</sup> which has however not been demonstrated to slow TKI metabolism.

### Discussion

Imatinib may cause vasodilatation and fluid retention due to inhibition of the PDGFR kinase that regulates interstitial fluid pressure. *PDGFRβ*- and *PDGFRβ*-knockout mice exhibit haemorrhages and oedema.<sup>3</sup>

We propose a possible second trigger for adverse effects related to fluid retention, namely garlic and chillies. These are found in chakalaka (isiZulu for 'chilli and tomato dish'), a popular traditional spicy relish. It contains chilli, garlic, tomatoes, green chilli peppers, grated carrots and cabbage, with beans or diced cauliflower. It is mostly home-made, but also available as a genetically modified organism-free canned product.

Chillies (*Capsicum annuum*) contain the strongly vasodilatory capsaicin. Capsaicin binds to the TRPV1 channel (transient receptor potential channel A1 or vanilloid receptor 1) (Fig. 1), which stimulates capsaicin-sensitive primary efferent neurons that project to cardiovascular and renal tissues.<sup>6,7</sup> This causes secretion of stored neurotransmitters, calcitonin gene-related peptide (CGRP) and substance P, which are potent vasodilators.<sup>7</sup>

Garlic contains the pungent organosulphur compounds alliin and diallyl disulphide (DADS). Alliin and DADS induce inflammation and pain by activating TRPA1, an excitatory ion channel on primary sensory neurons in the pain pathway.<sup>8</sup> These are the same neurons that respond to capsaicin. The vasorelaxation induced by DADS and alliin is probably mediated by the release of calcitonin gene-related peptide (CGRP) from capsaicin-sensitive nerve terminals.<sup>8</sup> Garlic also contains ajoene, a potent vasorelaxant.

The clinical improvement seen after withdrawal of the above substances would support the role of one or more of these compounds in side-effects related to fluid retention. Pharmacokinetic interactions that may have led to increased doses of the TKIs cannot be excluded. Some complementary and alternative medicines (CAMs) influence imatinib pharmacokinetics. St John's wort, garlic, kava-kava, ginseng and rapeseed extract decrease imatinib plasma levels by inducing *CYP3A4*. Further studies, including the determination of plasma levels of TKIs during exposure to herbal compounds, may elucidate the reactions we observed.

About 25% of the world's population eats hot chillies daily.<sup>5</sup> It is highly probable that interaction may occur between these and TKIs. Fluid retention may require reduction of the imatinib dose, with reduced therapeutic effect. It is therefore important

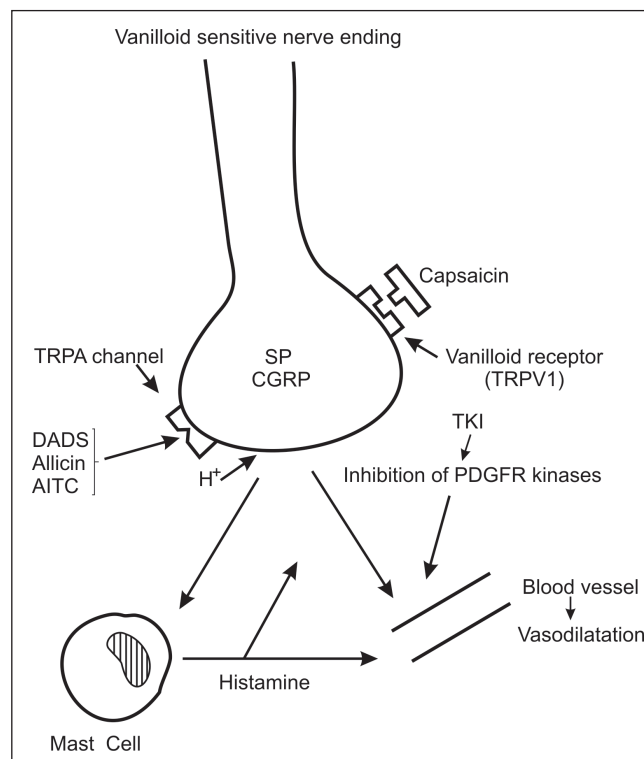


Fig. 1. The proposed mechanism of vasodilatation after exposure of a vanilloid-sensitive nerve ending to capsaicin or garlic and TKIs. Capsaicin binds to the vanilloid receptors TRPA1 (transient receptor potential channel A1). DADS (alliin and diallyl disulphide), alliin and AITC (allyl isothiocyanate) all bind the TRPA1 (transient receptor potential A1) channel. Both stimulate substance P (SP) and calcitonin gene-related peptide (CGRP), which cause vasodilatation. Stimulated mast cells release histamine, which also contributes to vasodilatation. TKIs contribute to vasodilatation by inhibiting PDGFR (platelet-derived growth factor receptor) kinases. (After Szallasi and Blumberg.<sup>7</sup>)

to ask about intake of spice and garlic when a patient on TKIs presents with oedema or headaches. Most patients using CAMs together with their oncotherapeutic drugs do not tell their doctor, so it is advisable to ask about these too. Further studies are needed to examine the interplay between TKIs and food substances.

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