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Review

Insight in taste alterations during treatment with protein kinase inhibitors

A. van der Werf [a,b,1], M. Rovithi [a,c,1], J.A.E. Langius [b,d], M.A.E. de van der Schueren [b,e], H.M.W. Verheul [a,*]

[a] *Department of Medical Oncology, Cancer Center Amsterdam, VU University Medical Center, P.O. Box 7057, 1081 HV, Amsterdam, The Netherlands*
[b] *Department of Nutrition and Dietetics, Internal Medicine, VU University Medical Center, P.O. Box 7057, 1081 HV, Amsterdam, The Netherlands*
[c] *Medical Oncology Unit, Department of Internal Medicine, Agios Nikolaos General Hospital, Const. Paleologos & Knossos, PC 72100, Agios Nikolaos, Crete, Greece*
[d] *Department of Nutrition and Dietetics, Faculty of Health, Nutrition and Sport, The Hague University of Applied Sciences, P.O. Box 13336, 2501 EH, The Hague, The Netherlands*
[e] *Faculty of Health and Social Studies, Department of Nutrition and Health, HAN University of Applied Sciences, P.O. Box 6960, 6503 GL, Nijmegen, The Netherlands*

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Abstract The role of Protein Kinase Inhibitors (PKI) in the treatment of various types of cancer is increasingly prominent. Their clinical application is accompanied by the development of side effects, among which patient-reported taste alterations. These alterations are missed frequently, but impair nutritional intake, are associated with weight loss and often result in significant morbidity, especially in the context of chronic administration. Accurate reporting of taste alterations is hampered by lack of modules for symptom objectification and inadequate understanding on the underlying mechanisms. In this review we initially describe the physiology of taste and smell and the mechanism of action of PKIs. We proceed to summarize taste related side effects as reported in major clinical trials and describe possible causal factors. Lastly, an in-depth analysis is given on potential molecular pathways responsible for the PKI-

* *Corresponding author.*
E-mail addresses: an.vanderwerf@vumc.nl (A. van der Werf), m.rovithi@vumc.nl (M. Rovithi), j.langius@vumc.nl (J.A.E. Langius), m.devanderschueren@vumc.nl (M.A.E. de van der Schueren), h.verheul@vumc.nl (H.M.W. Verheul).
[1] These authors contributed equally.

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induced taste alterations. Objectification of patient-reported symptoms and universal reporting, along with a better understanding of the underlying mechanisms, will lead to early recognition and optimized treatment, ultimately improving patient adherence and quality of life.
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1. Introduction/background

In the last decade, our increasing insight in the underlying biology of tumorigenesis has revealed distinct pathways that support tumour growth and sustain angiogenesis. Precision blockade of these pathways leads to increased tumour vulnerability and provides the scientific rationale for the development of targeted agents. Protein kinase inhibitors (PKIs) constitute a paradigm category of this class of anticancer agents that act by blocking the intracellular kinase domain of growth receptors or intracellular kinases, thereby inhibiting downstream signalling. Several PKIs have supplanted long-established chemotherapeutic agents and have been approved as standard of care in various treatment lines in the disease course. Clinical application showed their potential to improve patient survival and induce long term disease stabilization in a variety of tumour types. Despite the initial expectations of exclusive tumour cell specificity as opposed to conventional chemotherapeutics, adverse events have been increasingly reported. Chronic administration and subsequent prolongation of survival make the recognition and treatment of these side-effects throughout the treatment period imperative, in order to maintain an appropriate risk/benefit ratio [1–4].

One of the most commonly reported side-effects of PKIs is taste alteration, often referred to as dysgeusia. Taste alterations impair nutritional intake and influences quality of life in patients with cancer [5–8]. Reporting of this side-effect is usually limited to subjective descriptions of alterations; taste function has never been objectively assessed in patients receiving PKIs. The reported prevalence of PKI-induced patient-reported taste alterations varies depending on the type of PKI and treatment dose (Table 1). Examples include sunitinib, a Vascular Endothelial Growth Factor Receptor (VEGFR) inhibitor, with a prevalence of patient-reported taste alterations varying from 18% [9] to 63% [10] and vismodegib, a Hedgehog signalling pathway inhibitor, with a reported prevalence varying from 19% [11] to 85% [12].

The course of taste alterations has been described in a few studies. Development of oral adverse events was described to develop in 1–15 weeks after introduction of sunitinib or sorafenib [13]. In the majority of patients treated with vismodegib, patient-reported taste alterations developed within the first month after initiation and reversed within one month after discontinuation of treatment [12].

Although data on prevalence and the course of patient-reported taste alterations have been reported, more detailed data remain limited. The nature of the these alterations is not consistently described and may involve taste loss or taste hypersensitivity, as well as taste alteration, including a metallic, bitter, sour or salty taste [5]. Furthermore, the potential contribution of concurrent smell alterations has been inadequately recognised and recorded. This may be caused by the inconsistency among different trials in recording, reporting and scoring of patient-reported taste alterations while discrepant terminology further smothers the exact prevalence [14]. In addition, there are no consensus recommendations regarding objectification and monitoring of the symptoms.

Simultaneously with lack of routine objectification of described symptoms, effort dedicated to unravelling the underlying pathobiology remains limited. Nevertheless, the different manifestations, symptoms, clinical presentations and treatment of oral side-effects caused by targeted agents compared to 'traditional' chemotherapy, hint at the possibility of different pathobiology [14].

Table 1
Examples of PKIs and reported prevalence of patient-reported taste alteration.

PKI	Primary target [30]	Daily dose	Prevalence taste alterations
Imatinib	ABL, KIT, PDGFR	400 mg	3–13% [54–56]
		600 mg	14% [54]
		800 mg	NR
Dasatinib	ABL, Src	100 mg	NR
		140 mg	NR
		≥200 mg	3–10% [57]
Erlotinib	EGFR	150 mg	6% [58]
Gefitinib	EGFR	250 mg	NR
		500 mg	10% [59]
Osimertinib	EGFR	80 mg	NR
Sunitinib	KIT, VEGFR, FLT3	37.5 mg	20%
		50 mg	18–63% [9,10,60–64]
Sorafenib	VEGFR, BRAF	800 mg	3–55% [63,65–69]
Vismodegib	SMO	150 mg	19–85% [11,12,70–72]
Crizotinib	ALK, c-Met, ROS1	500 mg	11–26% [73–75]

ABL: ALK: anaplastic lymphoma kinase. EGFR: epidermal growth factor receptor. FLT3: fms-like tyrosine kinase receptor-3. PDGFR: platelet-derived growth factor receptor. SMO: smoothened homologue. VEGFR: vascular endothelial growth factor receptor.

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