Cabozantinib-Induced Dysgeusia in Oncology Trials: Strategies for Improved Outcomes

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ABSTRACT

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| Cabozantinib, a potent tyrosine kinase inhibitor (TKI), targets vascular endothelial growth factor receptor(VEGFR), mesenchymal-epithelial transition factor (MET), and AXL receptor tyrosine kinase to inhibit tumour angiogenesis, metastasis, and proliferation in advanced renal cell carcinoma (RCC). While oral administration enhances patient adherence, cabozantinib is frequently associated with dysgeusia, which can impact nutrition, treatment compliance, and quality of life. In the CABOSUN trial, 41% of patients reported dysgeusia, with broader studies indicating a prevalence of 56.3% among chemotherapy patients. The mechanisms underlying cabozantinib-induced dysgeusia involve VEGFR-mediated vascular disruption in taste buds, EGFR-related epithelial toxicity, and MET/AXL-induced salivary dysfunction. Zinc deficiency may further exacerbate symptoms. Management strategies include dietary modifications, oral hygiene interventions, salivary stimulation, and zinc supplementation. In refractory cases, dose adjustments may be necessary. Given the significant impact on patient well-being, a multidisciplinary approach is essential for optimising management. Future research should focus on standardised treatment guidelines and predictive biomarkers to mitigate dysgeusia and improve cancer care outcomes. |

*Keywords: cancer treatment toxicity, tyrosine kinase inhibitors (tkis), oncology trials, dysgeusia, cabozantinib*

1. INTRODUCTION

Cabozantinib is a potent tyrosine kinase inhibitor (TKI) that targets multiple receptor tyrosine kinases, including the vascular endothelial growth factor receptor (VEGFR), the mesenchymal- epithelial transition factor (MET), and the AXL receptor tyrosine kinase (Santoni et al., 2021). By inhibiting these key pathways, cabozantinib effectively disrupts tumor angiogenesis, suppresses metastasis, and inhibits cell proliferation (Grüllich, 2018). These mechanisms contribute to its efficacy in treating several malignancies, particularly advanced renal cell carcinoma (RCC), medullary thyroid carcinoma (MTC), and hepatocellular carcinoma (HCC) (Chan et al. 2024; Tutunaru et al., 2024). Cabozantinib affects not only the tumor microenvironment but also directly acts on the tumor cells, making them more susceptible to immune-mediated killing (Tokura et al., 2025; Bruchbacher et al., 2024). The oral administration of cabozantinib is a significant advantage in oncology treatment, providing greater convenience for patients and enhancing adherence compared to intravenously administered agents (Konda et al., 2025; Sepe et al., 2023).

Despite its clinical benefits, cabozantinib—like many TKIs—is associated with a wide range of adverse effects, many of which can impact patient quality of life and influence treatment adherence (Schmidinger & Danesi, 2018). One frequently reported but often underappreciated side effect is dysgeusia, or distortion or loss of taste (McGregor et al., 2022). Dysgeusia can begin subtly but is deeply disruptive to a patient's daily life, affecting not only food enjoyment but also appetite, nutritional status, and social behaviors related to eating. Over time, this can contribute to weight loss, malnutrition, and reduced tolerance to ongoing therapy.

In the CABOSUN trial (Choueiri et al., 2018), which compared cabozantinib with sunitinib in patients with untreated metastatic RCC, 41% of patients treated with cabozantinib reported experiencing dysgeusia. This finding is consistent with broader oncology research, which reveals that taste disturbances are not isolated to any single chemotherapeutic class. A review of 14 clinical studies found a weighted prevalence of 56. 3% for dysgeusia among chemotherapy patients (Hovan et al., 2010). Both studies highlight the significant impact of taste alterations on patients’ quality of life, though this issue remains insufficiently explored in the context of cabozantinib. Despite the high prevalence of dysgeusia and its potential to compromise nutritional status and treatment adherence, clinical guidelines for managing cabozantinib-induced dysgeusia are lacking. To date, there are no universally accepted strategies for preventing or treating this side effect. As a result, patients may endure prolonged discomfort or adopt suboptimal coping strategies, potentially leading to dose reductions or discontinuation of an otherwise effective therapy.

The mechanisms underlying cabozantinib-induced dysgeusia are not clear (Yavuz et al., 2014). They are multifactorial, involving a variety of interconnected biological processes. One of the primary actions of cabozantinib is the inhibition of vascular endothelial growth factor receptor (VEGFR), which disrupts the vascular supply to the taste buds. This disruption can potentially lead to atrophy of these crucial sensory organs, thereby diminishing the ability to perceive taste (Epstein and Barasch, 2010). Additionally, the blockade of the epidermal growth factor receptor (EGFR) significantly impairs the turnover of epithelial cells, thereby exacerbating the toxicity experienced in the mucosal layers of the oral cavity (Zuo et al., 2015). Furthermore, the inhibition of MET and AXL receptors, which play vital roles in maintaining salivary gland function, alters the overall composition of saliva. This alteration can further impair taste perception by reducing the mouth's ability to function effectively in the tasting process. Moreover, it has been suggested that cabozantinib may also induce a zinc deficiency (Najafizadeh et al., 2013), a mineral known to be a significant contributor to taste disturbances. This potential deficiency may exacerbate the severity of dysgeusia experienced by patients, resulting in a more pronounced impact on their quality of life due to the altered taste sensation

Furthermore, the poor recognition of dysgeusia in clinical practice may stem from its subjective nature and the lack of standardised assessment tools. "Toxicities such as hypertension and diarrhea are thoroughly graded and closely monitored using standardised tools like the Common Terminology Criteria for Adverse Events (Cancer Therapy Evaluation Program, 2017), which provides a systematic framework for assessing and documenting adverse effects in clinical trials. However, taste disturbances, a common yet often overlooked side effect, could be underreported or minimised during clinical encounters. This could be partly due to the limitations of the CTCAE, which primarily captures grade 1 and 2 toxicities while leaving grades 3, 4, and 5 unaddressed (Cancer Therapy Evaluation Program, 2017). As a result, the tool may fail to fully capture the severity and impact of taste disturbances on patients' quality of life. This gap in the assessment may contribute to a lack of emphasis on taste disturbances as a serious side effect, preventing appropriate management and intervention.

This poses significant problems, particularly in light of the growing emphasis on patient-centered care and quality of life as key outcomes in oncology. The absence of systematic consideration for dysgeusia in clinical trials hinders the creation of targeted interventions and leads to its ongoing sidelining in the management of cancer symptoms. This concern goes beyond mere underreporting; taste disturbances are often deemed less critical compared to the more urgent health threats that cancer brings. As a result, dysgeusia frequently lacks the necessary focus and prioritisation in enhancing the overall patient experience throughout cancer treatment.

The rising application of cabozantinib for advanced cancers amplifies this issue. With cancer care evolving toward chronic treatment, the long-term tolerability of drugs like cabozantinib becomes as vital as their efficacy. For patients who may be on treatment for months or years, ongoing dysgeusia can jeopardise therapeutic goals, leading to unnecessary treatment discontinuations or dosage reductions. This issue is particularly pertinent in real-world situations, where managing side effects can differ significantly from the controlled conditions of clinical trials.

2. Clinical Impact of Dysgeusia on Patient Quality of Life

While the primary aim of these therapies is to manage cancer progression, the resulting side effects, particularly those affecting sensory perception like dysgeusia, can significantly impact patients' overall quality of life. Dysgeusia alters taste perception, affecting how patients experience food and leading to profound physical, psychological, and social consequences.

It significantly impacts a patient’s psychological and emotional health (Mazzoleni et al., 2024), a factor that is often underestimated. The loss of enjoyment in food, one of life's simple pleasures, can lead to feelings of frustration, helplessness, and isolation. Food serves not only as a source of sustenance but also as a cultural and emotional cornerstone, connecting individuals to their families, memories, and social rituals (Lynch, 2025). When patients lose the ability to enjoy food due to taste disturbances, it can trigger feelings of deprivation and sadness, potentially escalating into more serious mental health issues, such as depression and anxiety. Patients often describe the frustration of trying to eat food they once enjoyed, only to find the taste metallic, bitter, or otherwise unpleasant. This phenomenon can heighten stress, as patients feel alienated from a fundamental human experience—eating.

The emotional toll of consistently dealing with unpleasant food experiences can lead to withdrawal from social situations where meals are typically shared among family and friends. This isolation can exacerbate loneliness, particularly in patients already confronting the trauma and uncertainty of cancer treatment. The frustration of not being able to enjoy food can also result in anxiety about eating, as patients may begin to associate mealtimes with distress rather than nourishment. Moreover, the uncertainty of the future due to cancer and its treatment often leads patients to focus emotionally on managing side effects. Dysgeusia thus becomes not just a physical burden but also an emotional one, as patients may feel as though they are losing control over their bodies in a way that is both distressing and alienating.

The inability to predict which foods will be palatable day by day further adds to this psychological burden, leading to emotional exhaustion. One direct consequence of dysgeusia is its effect on appetite and nutritional intake (Kulsoom, Krawczyk, & Gupta, 2025). Patients with taste disturbances often report a decreased desire to eat, as foods that once provided comfort and satisfaction may now seem unappetising or even repulsive. This decline in appetite is especially concerning, as maintaining proper nutrition is critical during treatment. Weight loss and malnutrition are common outcomes of this reduced intake (Kulsoom, Krawczyk, & Gupta, 2025), which can further impair a patient’s ability to tolerate treatment, leading to delays or the need to discontinue therapy entirely. The frustration of not being able to nourish oneself due to dysgeusia can amplify feelings of losing control over one’s body. Patients may feel that their illness and treatment have taken away yet another important part of their lives, intensifying the emotional toll of cancer treatment. As weight loss progresses, it can lead to muscle wasting and impaired immune function, further weakening the patient’s resilience and ability to cope with the side effects of chemotherapy or targeted therapies.

In some cases, the cumulative effects of poor nutrition can increase the risk of infections and other complications, ultimately leading to prolonged hospital stays or a greater reliance on medical interventions. This negative cycle of dysgeusia-induced malnutrition can ultimately influence the patient’s overall prognosis, as adequate nutrition is essential for supporting immune function, wound healing, and recovery. Patients unable to maintain a healthy weight or nutritional status may experience a reduced response to cancer treatments, including chemotherapy, immunotherapy, and TKIs, which can compromise their survival outcomes. This creates a vicious cycle where dysgeusia both directly and indirectly worsens the patient's cancer prognosis.

In clinical practice, many patients report that the severity of dysgeusia leads them to discontinue their cancer therapies prematurely or to request dose reductions to alleviate distressing symptoms (Syed et al., 2016). This is particularly true for treatments with long durations, such as TKI therapies, which are often administered for months or even years. For example, a patient undergoing treatment for metastatic renal cell carcinoma with cabozantinib may experience significant taste changes that lead to decreased treatment adherence. As the patient struggles to tolerate food and nutrition, their physical strength may decline, leaving them feeling more fatigued and less able to manage the side effects of the drug. At this juncture, they may choose to delay or stop treatment altogether, believing that the burden of dysgeusia outweighs the therapy's benefits. This decision, though understandable from a quality-of-life perspective, can be detrimental to the patient’s prognosis if it results in tumor progression or other complications from halted treatment.

An important aspect of managing cancer-related side effects is addressing them early in the treatment regimen to prevent unnecessary interruptions. In some cases, the constant cycle of taste disturbances combined with weight loss and poor nutritional intake can induce anxiety around food and mealtimes. Patients may become anxious about trying new foods or even preparing meals, fearing they will experience overwhelming, unpleasant tastes again. This can lead to avoidance behaviors, where patients refuse to eat altogether or limit their diet to a narrow range of foods that may not satisfy their nutritional needs. The anxiety surrounding food choices and mealtimes can add another layer of emotional strain, exacerbating feelings of stress and loss of control.

**3. STRATEGIES FOR MANAGING CABOZANTINIB-INDUCED DYSGEUSIA**

Clinicians must recognise the significant toll that dysgeusia can take on a patient's motivation to continue treatment and work proactively to implement strategies for alleviating the symptoms. If dysgeusia is not addressed, patients may miss out on the full benefits of potentially life-saving therapies due to non-adherence or treatment abandonment.

To effectively mitigate dysgeusia and improve patient adherence to cancer treatments, a broad range of personalised interventions can be employed, each targeting specific aspects of the sensory disturbances associated with treatment. Dysgeusia, or the alteration of taste perception, is a common and distressing side effect of chemotherapy and other cancer therapies, particularly in patients undergoing treatments like cabozantinib. Since these taste changes significantly impact a patient’s quality of life, appetite, and nutritional intake, addressing this symptom is critical not only for improving patient comfort but also for enhancing treatment adherence.

One key approach involves modifying the sensory experience of eating. For instance, the use of plastic utensils, as opposed to metal ones, can prevent the intensification of bitter or metallic tastes that are common with dysgeusia (Brown, n.d.). Similarly, incorporating marinades and citrus-based flavors can mask unpleasant tastes and stimulate the taste buds, making food more palatable for patients. Additionally, consuming cold or room-temperature foods rather than hot foods can help reduce the intensity of taste alterations. These modifications are practical and can be easily incorporated into the patient’s daily routine, offering relief from the debilitating effects of altered taste perception.

Beyond dietary changes, oral hygiene plays a crucial role in managing dysgeusia. Research suggests that maintaining good oral hygiene practices can reduce the severity of taste disturbances and promote a more comfortable eating experience. Measures such as baking soda rinses can help neutralise the pH of the oral cavity, reducing the metallic taste that many patients report. Other interventions, such as using olive oil and sucralfate mouthwashes, can provide a soothing effect to the oral mucosa, addressing both discomfort and altered taste sensations. Doxycycline mouthwash (two tablets dissolved in 250 mL of water) has also been shown to be beneficial in improving taste function by reducing oral inflammation and bacterial load, which may contribute to taste changes (Schmidinger and Danesi, 2018; Hovan et al., 2010). Triamcinolone acetonide ointment, a corticosteroid, can help reduce inflammation and oral discomfort, providing further symptomatic relief for patients experiencing severe taste alterations.

Another promising therapeutic intervention involves the use of zinc supplementation. Zinc is an essential trace element that plays a crucial role in maintaining normal taste function. A randomised controlled trial demonstrated that a daily dose of 220 mg of zinc sulfate significantly improved taste acuity in patients undergoing chemotherapy, suggesting that zinc deficiency or disruption in zinc metabolism might be contributing factors to taste alterations (Najafizadeh et al., 2013). While this intervention has not been specifically studied in patients with cabozantinib-induced dysgeusia, the positive results observed in chemotherapy patients point to the potential benefits of zinc supplementation for improving taste perception in a broader oncology context. The inclusion of zinc as part of a comprehensive treatment plan may offer substantial benefits for patients experiencing taste changes during cancer treatment.

Moreover, enhancing salivary flow is another avenue for managing dysgeusia. Reduced saliva production is often a contributing factor to the severity of taste disturbances, as it impairs the oral cavity's ability to neutralise acids and deliver essential nutrients to the taste receptors. Methods aimed at stimulating salivary flow, such as chewing sugar-free gum or using saliva substitutes, can help restore taste function by enhancing salivary secretion and maintaining a balanced oral pH. These approaches not only help mitigate the sensory impairment caused by dry mouth but also provide relief for patients who experience discomfort during eating (Matsuo, 2000). Encouraging the use of saliva stimulants as part of a broader symptom management strategy can be particularly beneficial for patients undergoing treatments that reduce salivation.

In more severe cases where supportive care and non-pharmacological interventions fail to provide sufficient relief, adjusting the patient’s treatment regimen may become necessary. In the case of cabozantinib-induced dysgeusia, reducing or temporarily ceasing the medication may be considered, particularly if the severity of the disturbance significantly impacts the patient's quality of life or nutritional intake. However, such decisions must be approached with caution, as the therapeutic efficacy of the drug must be weighed against its tolerability. Maintaining a balance between optimising cancer treatment and managing side effects is crucial, and this requires a personalised approach to care that considers the individual needs and circumstances of each patient.

Ultimately, the management of dysgeusia in oncology patients should involve a comprehensive, individualised approach. This approach should not only include dietary and oral hygiene interventions but also consider pharmacological treatments and methods to stimulate salivary flow. By addressing dysgeusia from multiple angles, healthcare providers can significantly improve the patient’s experience during cancer treatment, enhance their nutritional intake, and increase the likelihood of treatment adherence. With a thoughtful and personalised treatment plan, dysgeusia can be effectively managed, thus allowing patients to focus on their recovery and well-being while minimising the burden of this underappreciated side effect

**4. CONCLUSION**

In conclusion, cabozantinib is a potent tyrosine kinase inhibitor with significant efficacy in treating various malignancies, including advanced renal cell carcinoma, medullary thyroid carcinoma, and hepatocellular carcinoma. However, like many targeted therapies, it is associated with a range of adverse effects, notably dysgeusia, which can significantly affect patients' quality of life. The mechanisms underlying this side effect, including the disruption of taste bud function and alterations in salivary composition, are multifactorial and not yet fully understood. Despite the high prevalence of dysgeusia, clinical recognition and management of this symptom remain inadequate, with no standardised guidelines for its prevention or treatment. This underappreciation of dysgeusia can lead to suboptimal patient outcomes, including decreased treatment adherence, malnutrition, and potential treatment discontinuation.

The growing use of cabozantinib in chronic cancer care underscores the need for proactive management of side effects like dysgeusia, as it can impact long-term therapy adherence and patient well-being. Interventions such as dietary modifications, improved oral hygiene, and zinc supplementation offer potential relief and may improve patient comfort and adherence. In some cases, adjustments to the treatment regimen may be necessary to balance efficacy and tolerability. Addressing dysgeusia and other similar symptoms is crucial for enhancing the overall patient experience, ensuring the continued effectiveness of cancer therapies, and improving the quality of life for patients undergoing long-term treatment with agents like cabozantinib.

Consent

Not applicable

Ethical approval

Not applicable.

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