Biol Blood Marrow Transplant 24 (2018) 425–432

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Reviews

Unlocking the Complex Flavors of Dysgeusia after Hematopoietic Cell Transplantation

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Article history:
Received 10 August 2017
Accepted 9 October 2017

Key Words:
Taste disturbances
Dysgeusia
Hematopoietic cell transplantation

A B S T R A C T

Dysgeusia is a frequently occurring symptom after hematopoietic cell transplantation (HCT) that has important long-term effects on physical, nutritional, and immunologic recovery, as well as on quality of life. Despite the relevance of this symptom, the study of dysgeusia in patients undergoing HCT has been limited, owing in part to its complexity. In this article, we review normal taste function and its clinical evaluation, discuss how dysgeusia uniquely affects patients undergoing HCT, and examine distinct, transplantation-related contributors to dysgeusia that may help elucidate strategies to ultimately reduce this symptom burden after transplantation.

INTRODUCTION

Taste disturbance, known as dysgeusia, is an often-reported yet underappreciated sequela of cancer therapy that can markedly affect patients' quality of life (QoL) [1]. Although dysgeusia is not unique to recipients of hematopoietic cell transplantation (HCT), this complication may be most pertinent in the early post-transplantation period, when direct conditioning regimen-related mucosal injury impairs taste and flavor perception and alters nutritional absorptive capacity, and when myelosuppression and delayed immune recovery affect mucosal immunity and oropharyngeal microbiome biodiversity [2-6]. Moreover, distinct transplantation-related complications, such as graft-versus-host disease (GVHD), can further negatively affect taste perception [7,8]. All of these contributing factors impede the nutritional intake needed to promote physical and emotional recovery as well as adequate immune reconstitution.

Although transplantation physicians often find themselves discussing taste disturbances with their patients, the pathophysiology of dysgeusia is poorly understood, and to our knowledge, has not been widely evaluated in prospective HCT clinical trials. As the number of annual transplantations performed continues to grow and the number of older long-term survivors increases, we feel it is essential to focus attention on this complication [9,10]. In this report, we review normal taste function and how it is evaluated, discuss unique transplantation-related factors that contribute to dysgeusia, and examine potentially novel strategies for studying and mitigating dysgeusia in this patient population.

Review of Taste Function

At its fundamental level, the sense of taste has evolved to allow an individual to appraise ingested items as nutritious food or noxious material. It also allows one to derive satisfaction and pleasure from the experience of eating [11]. As such, taste plays a critical role in both nutritional status and QoL. Human flavor perception is a highly regulated and multicomponent sensorial system that involves neuronal pathways, the sense of olfaction, and adequate saliva production [8]. At the time of food consumption, salivary enzymes dissolve taste molecules that are delivered to taste receptors. Multiple taste receptor cells contained within taste buds of the tongue, palate, and oropharynx function as neuroreceptors. Three distinct types of taste receptor cells are thought to transduce specific taste stimuli. All of these subtypes turn over every 10 to 14 days, when they undergo apoptosis and are

Financial disclosure: See Acknowledgments on page 430.
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https://doi.org/10.1016/j.bbmt.2017.10.022
1083-8791/

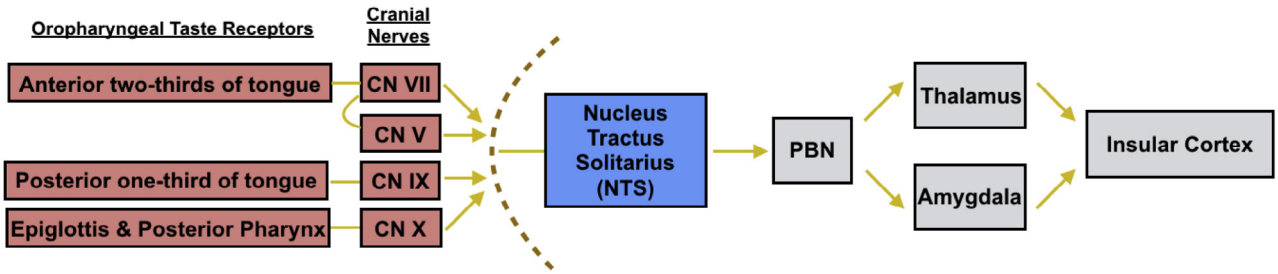

Figure 1. Schematic of the basic taste pathway. This simple schematic (not every aspect of this complex pathway is shown) shows the basic taste pathway. Taste molecules stimulate taste receptors, located on taste buds in the oropharynx. These taste signals are carried by afferent nerve fibers of cranial nerves (CN) with branches converging at the nucleus tractus solitarius (NTS). The gustatory signal then projects to the parabrachial nucleus (PBN) in the pons. From there, connections are made in the thalamus, amygdala, and insular cortex of the brain where this complex system is integrated into a gustotopic map corresponding to specific taste qualities. (Adapted from references 11, 13, and 18).

continually renewed [12]. Stimulation by molecules of ingested food leads to signaling that is mediated by G-protein-coupled receptors and nerve depolarization through sensory afferent pathways of cranial nerves VII (facial), IX (glossopharyngeal), and X (vagus), as well as a portion of the mandibular branch of V (trigeminal), that converge on the nucleus tractus solitarius of the medulla and through the parabrachial nucleus [1,11,13]. They subsequently connect in the thalamus, amygdala, and insular cortex of the brain, where this complex system is integrated into a gustotopic map with distinct neuronal areas that correspond to specific taste qualities [14,15]. A schematic of the basic taste pathway is illustrated in Figure 1. Further complexity is added to this neuronal system by the contributions of orthonasal and retronasal olfaction during mastication, which are easily identifiable clinically by any person who has previously experienced flavor disturbances with a loss of the sense of smell [16,17]. The intricacies of these neuronal networks help explain some of the difficulty treating dysgeusia, given the numerous potential etiologies that can affect taste perception along any of these pathways [1].

There are at least 5 basic human taste qualities that identify unique chemical qualities in food: sweetness, bitterness, saltiness, sourness, and a more recently described taste known as umami that recognizes savory, glutamate-rich foods. Less well-defined taste qualities, such as spiciness and oleogustus ("fattiness"), among others, can add flavor depth to the experience, along with the contributions of retro-olfaction as mentioned above [1,11,18,19]. Patients being treated for cancer commonly report loss of specific taste qualities; however, they often describe a chronic bitter or metallic taste that affects the flavor of all ingested foods and liquids [20].

Causes of Taste Disorders in Patients with Cancer

Taste disorders in patients with cancer are often have multiple etiologies [19]. Patients with head and neck cancer undergoing multimodal treatment with surgery, chemotherapy, and radiotherapy (RT) are the most well-studied population [21]. A 75% to 100% incidence of taste disturbances in this population has been reported in several series, with some patients describing taste changes even before the start of treatment, suggesting a direct impact of the tumor [22]. In a mouse model developed by Nguyen et al. [12], in which taste buds were disrupted by radiation exposure, the primary mechanism of taste disturbance after RT was direct injury to taste receptor progenitor cells that impeded normal cell turnover. In addition, RT damages salivary glands, resulting in hyposalivation and often painful naso-oropharyngeal mucositis, which may exacerbate taste dysfunction [23]. Along with direct injury to the oral mucosa and tongue epithelium, surgery and RT also can affect taste through injury to the larger cranial nerves described above. These multifactorial mucosal effects are often further compounded by concurrent cytotoxic and targeted chemotherapies, as well as by supportive medications that damage rapidly diving taste receptor cells, impact salivation, and cause neuropathy [24-26]. Moreover, numerous supportive medications with different mechanisms of action have been reported to cause reversible taste disorders, including antimicrobials, diuretics, and antihypertensives, all of which are frequently used after HCT [27-29].

Unique Aspects of Taste Disturbances in Patients Undergoing HCT

Conditioning regimens

The contributors to dysgeusia may differ between recipients of autologous stem cell transplantation (ASCT) and recipients of allogeneic HCT (allo-HCT) [30,31]. Early taste disturbances after ASCT are largely caused by direct conditioning regimen-related oral mucosal and salivary gland injury from chemotherapy with or without RT. A patient's underlying disease often dictates the choice of conditioning regimen, which in turn variably affects the severity and duration of dysgeusia and decreased saliva production. The most common indications for ASCT are multiple myeloma and non-Hodgkin lymphoma, for which high-dose melphalan and combination chemotherapy regimens, such as carmustine, etoposide, cytarabine, and melphalan (BEAM), are widely used [32,33]. A recent retrospective analysis of patients with lymphoma and myeloma receiving a BEAM-like regimen and high-dose melphalan, respectively, identified both combination chemotherapy conditioning regimens and the development of oral mucositis as independent risk factors for dysgeusia [34]. Patients with myeloma who received oral preventive cryotherapy before high-dose melphalan therapy were at less risk of significant taste disturbances. No other patient or transplantation characteristics were found to modulate the risk of developing dysgeusia. Moreover, nutritional intake measurements confirmed that patients who developed dysgeusia had lower total caloric intake and more frequently required total parenteral nutrition [34].

Late effects on taste after ASCT appear to be largely a function of residual conditioning regimen effects, unwanted side effects of supportive medications, and other ordinary causes of smell loss and dysgeusia in patients with chronic disease [2,8].

For patients undergoing allo-HCT, dysgeusia appears to be a longer-lasting and more complex problem, perhaps due to the more intense conditioning regimens, exposure to immunosuppressants, and the increased frequency of infections and the alloreactive complications unique to this type of transplantation [30]. Whereas most chemotherapy-only myeloablative conditioning regimens pose a similar risk for taste disturbances and anorexia in allo-HCT recipients and ASCT recipients, total body irradiation (TBI)- based conditioning is used more often in allo-HCT and is associated with more profound mucosal injury. A common GVHD prophylaxis regimen uses methotrexate, which has well-known mucosal toxicity [35]. Even in the absence of methotrexate-containing GVHD prophylaxis regimens, TBI-based regimens are associated with mucositis rates of up to 64% [36].

GVHD

Several proinflammatory cytokines, including IL-2, IL-6, and TNF-α, have been reported to negatively affect appetite in patients with cancer [37]. In a study of allo-HCT recipients who received myeloablative conditioning, these cytokines were markedly increased in the early post-transplantation period, coincident with decreased oral intake. Interestingly, patients with persistent fever had the most significant reductions in measured oral intake [38]. In contrast, Mattsson et al. [39] found a significant correlation between the number of days without oral intake (which may reflect the severity of mucositis) and the development of severe GVHD. Based on their findings and on previous studies, the authors suggested that promoting enteral nutrition after allo-HCT might represent an opportunity to reduce the production of gut-associated proinflammatory cytokines and thereby potentially improve oral intake [39]. Although these studies support associations between GVHD and anorexia and reduced oral intake, whether these effects are mediated through taste disturbances is unclear. Surprisingly, taste acuity measured prospectively in 3 groups of patients at different time points after allo-HCT showed no association between taste disturbances and salivary output with concurrent incidence of chronic oral GVHD, although there were clear changes in taste perception that persisted as far as 3 years after allo-HCT in some patients [8]. These data highlight the need for further investigation of the role of GVHD in affecting normal taste.

Dysgeusia and malnourishment

Taste disturbances can have profound, objective effects on dietary intake and certain indicators of nutritional status after HCT, such as albumin. Hypoalbuminemia is a reflection of multiple factors, including liver synthetic function, the inflammatory cytokine milieu, and losses through proteinuria or protein-losing enteropathy, with nutritional status representing only one key component [40]. However, multiple studies have demonstrated an association between pretransplantation and post-transplantation albumin levels and the development of GVHD, nonrelapse mortality (NRM), and overall survival [40-42]. Hypoalbuminemia also contributes to post-transplantation volume overload, which is now recognized as an important adverse event with serious implications for NRM [43]. A deleterious cycle of intravascular fluid loss and marked interstitial edema due to hypoalbuminemia and impaired vascular tone clinically influences the use and overuse of intravenous (IV) fluids after transplantation, further exacerbating the problem, even in the absence of sepsis or overt critical illness [44,45]. In a study of 48 patients undergoing high-dose therapy and ASCT, 24 patients (42%) reported dysgeusia. These patients had poorer nutrition, with longer periods of decreased oral intake and more days requiring parenteral nutrition than those not reporting taste disturbances [34]. The presence of mucositis and the intensity of the conditioning regimen were independent risk factors for developing dysgeusia. The foregoing studies support the associations between taste disturbances and poor dietary intake, and suggest that dysgeusia may play an integral role in contributing to this cycle of poor nutrition, GVHD, and NRM.

Similarly, by decreasing the desire for oral intake, dysgeusia likely affects other surrogate measures of nutritional status after HCT, such as weight loss and body mass index (BMI). Patients considered malnourished based on these surrogate measures after HCT have inferior overall survival [46]. A large study reported by Navarro et al. [47] using data from the Center for International Blood and Marrow Transplant Research reported an increased risk of all-cause death in underweight patients compared with normal-weight patients. It should be noted that although weight and BMI are often used as surrogates of nutritional state, they imperfectly reflect the full biological assessment of nourishment. This may be particularly true as we develop a more robust understanding of the role of cardiopulmonary health, muscle mass, and physical conditioning on post-transplantation recovery and outcomes [46,48]. Diminished post-transplantation oral intake and progressive weight loss often necessitate the provision of nutrition support. Recent consensus guidelines from the United States and Europe have more clearly specified the importance of enteral nutrition (EN) over parenteral nutrition (PN) in patients after HCT [46,49]. An observational study using propensity score adjustment showed better overall survival and lower rates of acute GVHD in patients fed via EN compared with those receiving PN [50]. In a similar study, although Guieze et al. [51] found no overall survival difference, patients receiving EN had fewer days of fever, a reduced need for antifungal therapy, and less risk of transfer to a higher level of care. A highly relevant, prospective, randomized study comparing NRM rates between patients with hematologic malignancies receiving EN and those receiving PN after allo-HCT is currently ongoing (NCT01955772) [52]. Whether reductions in taste disturbances can further influence improvements in post-transplantation oral intake in patients has not yet been studied prospectively and merits investigation.

Immune recovery

By influencing appetite and nutritional intake, dysgeusia also indirectly impacts immunity, given the well-recognized relationships between malnutrition and weight loss, impaired healing, and ineffective innate and adaptive immune responses [53]. In the early post-transplantation period, immune recovery represents a critical step in avoiding life-threatening infections and risk of disease relapse [54]. The thymus maintains effective immune function, and thymic atrophy from malnourishment suppresses T cell maturation and function. This is particularly relevant in older adults, who naturally have thymic involution with advancing age, and in the context of conditioning regimen- and GVHD-related thymic injury after HCT [55-58]. Nutritional formulas designed to improve immune responses, also known as immunonutrition, have been studied in multiple populations, including critically ill patients, with mixed and sometimes negative results [59-61]. Interestingly, anorexia during infection is a widely recognized phenomenon thought by some to represent an adaptive response that up-regulates

and improves autophagy in immune and nonimmune cells [62]. Whether optimal timing of our nutritional efforts could maximize immune function after allo-HCT requires further inquiry.

The unique role of the microbiome

Recent advances in sequencing technology have allowed renewed investigations into the multifaceted and integral role of the human intestinal microbiota in health and disease [63]. Patients undergoing allo-HCT represent a distinctive group in which to study the intestinal microbiota, given their intense nutritional disturbances and antibiotic exposures. Conditioning regimens result in marked colonic mucosal injury, which allows for resulting gut translocation of microorganisms or their products, such as lipopolysaccharide, as well as poor nutritional intake and dysgeusia [64]. GVHD prophylaxis medications, prolonged exposure to antibiotics, and donor-host immunologic interactions all contribute to these complex interactions [65]. Reductions in intestinal flora diversity and the abundance of specific species within the intestinal lumen have been linked to such post-transplantation outcomes as GVHD, pulmonary complications, bacteremia, *Clostridium difficile* infection, relapse, and overall survival [5,66-70]. This is of particular interest given the burgeoning literature linking the impact of the human diet on modifying the gut microbiome and demonstrating how these microorganisms in turn influence nutritional habits and behavior [71,72].

Although most microbiome studies in the transplantation setting have focused on intestinal microbiota, the changes that occur in the oral microbiome during transplantation and their possible role in dysgeusia or other transplantation outcomes has not been well studied. Pilot data from our institution (reported in abstract form) suggest that oral bacterial biomass declines early after transplantation and increases following hospital discharge, and that most patients experience a significant shift in oral bacterial composition over the course of transplantation [73].

The role of oropharyngeal microbiota in the oral environment, specifically in oral mucositis and dysgeusia, remains unclear [74,75]. Given the immense diversity of the oropharyngeal flora and the known effects of the gastrointestinal microbiota, it stands to reason that the oropharyngeal microbiota plays a role in both mucositis and taste disturbances, and also may play a role in oral chronic GVHD [76]. Previous studies evaluating the role of oral microbes in the development of mucositis are confounded by patient, disease, and methodological heterogeneity [77,78]. The paucity of data on the role of oropharyngeal microbiota in affecting taste disturbances, nutrition, and outcomes highlights the need for further inquiry.

QoL

Only a few studies to date have quantified the symptom burden of dysgeusia. Sonis et al. [2] prospectively examined physical, emotional, and social function in 56 patients in their first year after HCT and found that 20% of patients reported dysgeusia that impacted QoL. Campagnaro et al. [79] prospectively evaluated the symptom burden of patients undergoing high-dose melphalan-based ASCT within the first 30 days using the M.D. Anderson Symptom Inventory—Blood and Marrow Transplantation (MDASI-BMT), and found that the most common early post-transplantation symptoms included fatigue, weakness, anorexia/nausea, diarrhea, and insomnia. Importantly, these symptoms were associated with decreased frequency of physical activity and QoL. Although many of the toxicities in this prospective study are interrelated, dysgeusia likely contributed in part to these symptom clusters [80,81]. Table 1 presents a summary of selected published trials of dysgeusia and related factors after HCT.

Assessment of Taste Dysfunction

A detailed patient history assessing the onset and quality of symptoms, medication review, and a comprehensive head and neck physical examination are invaluable tools in identifying the etiology of taste disturbances. Commercially available kits, such as the University of Pennsylvania Smell Identification Test (UPSIT), have been used to evaluate the contribution of olfactory disturbances to dysgeusia [1,82]. Relevant laboratory testing for electrolyte disturbances and for hepatic and renal function also may be indicated in certain cases; for example, hyperuricemia is known to be associated with appetite suppression [83].

Given the importance of flavor on QoL and adequate nutritional intake, it is essential to integrate both subjective and objective data when assessing dysgeusia after HCT. Several scoring systems have been used to quantify and quality dysgeusia, including the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and the Scale of Subjective Total Taste Acuity (STTA) [84,85]. Table 2 summarizes these 2 clinician-based tools for assessing taste disturbances. In addition, taste abnormalities can be obtained with patient-reported outcome instruments, such the National Cancer Institute's patient-reported outcome CTCAE, which can complement standard clinician toxicity reporting [85]. Chemical gustometry is an objective and standardized test for assessing taste function. In whole-mouth gustometric testing, the patient first rinses his or her mouth with room temperature water. Then small amounts of specific chemical reagents at various concentrations that test the 5 taste senses are swished around the mouth or applied directly throughout the tongue and mouth by soaked filter paper/applicators or droppers. Similarly, spatial taste testing allows the tester to compare taste changes in different areas of the oral cavity [1].

Given the known contributions of salivation on taste disturbances, additional complementary patient evaluations include salivary measurements, which objectively estimate the stimulated and unstimulated salivary flow rate. In the largest prospective study of chemical gustometry reported to date, Boer et al. [8] evaluated oral examination findings, taste changes, and salivary flow rate in 61 patients after allo-HCT. They found definitive taste alterations over an extended period post-HCT, supporting the idea that these changes often do not correlate with oral mucosal injury related to chronic GVHD and/or changes in salivary function. This study established the proof of principle that chemical gustometry and salivation rates can be studied systematically and prospectively, but also highlighted the difficulty in understanding specific pre-HCT and post-HCT patient characteristics that may contribute to oral pathology, given the heterogeneity of patients and diseases. Mucosal sensitivity that may represent mucosal atrophy or neuropathy, particularly of C-fibers, may affect diet [19]. Further oral evaluation includes assessment of oral hygiene and levels of dental plaque.

Prevention and Treatment

There are no specific and effective treatments for patients with dysgeusia. Several published studies of zinc supplementation have demonstrated modest improvements in taste disturbances, particularly in patients with

Table 1
Selected Published Trials of Dysgeusia and Related Factors after HCT

Study	Study Type	Type of HCT (No. of Patients)	Outcome/Findings
Dysgeusia and/or oral mucositis			
Marinone et al. (2001) [30]	Retrospective	ASCT (8); allo-HCT (15); normal subjects (20)	Allo-HCT: hypogeusia for salt; no variations for sweet and bitter ASCT: no variation for sweet, salt, sour
Cutler et al. (2005) [35]	Retrospective	Allo-HCT: MTX-based GVHD prophylaxis (24); non–MTX-based GVHD prophylaxis (30)	Mild, moderate, and severe mucositis (%): MTX group, 8%, 42%, and 50%, respectively; non-MTX group 37%, 57%, and 7%, respectively. Less TPN, less narcotic use in the non-MTX group; shorter hospitalizations.
Okada et al. (2016) [34]	Retrospective	ASCT (48)	Dysgeusia in 20 patients (42%); TPN rates higher in those with dysgeusia; combination chemotherapy and oral mucositis risk factors for dysgeusia; oral cryotherapy reduced dysgeusia.
Dysgeusia/nutrition and GVHD			
Boer et al. (2010) [8]	Prospective	Allo-HCT	Measured taste perception, salivation, and oral pathologies; taste alterations noted over long-term follow-up. Thirty-one patients had chronic GVHD; there was no correlation between taste dysfunction and oral chronic GVHD. Salivation was decreased in 16% of patients.
Malone et al. (2007) [38]	Prospective	Allo-HCT (147)	Determined oral intake, assessed cytokine levels and correlation with anorexia, Oral caloric intake was reduced in 92%. Plasma cytokines (IL-2, IL-6, TNF-α) abnormally elevated early post-HCT; patients with persistent fever had the greatest reduction in oral intake.
Mattsson et al. (2006) [39]		Allo-HCT (231)	Studied nutritional history of patients after allo-HCT. Patients with high-grade GVHD received more PN than those with low-grade GVHD. There was a correlation between the number of days without oral intake and incidence of acute GVHD; >9 days without oral intake was associated with high-grade GVHD (OR, 7.66; 95% CI, 1.44 to 40.7; $P = .016$)
Dysgeusia and anorexia/ malnourishment			
Seguy et al. (2006) [50]		Allo-HCT (45): Received enteral nutrition (22); received parenteral nutrition (23)	Those who received EN had less high-grade acute GVHD compared with those who received PN (18% versus 35%; $P = .011$). The EN group also had lower infection-related mortality.
Navarro et al. (2010) [47]	Retrospective	ASCT and allo-HCT (4215)	Patients were compared based on BMI. There was an increased risk of death in underweight patients in related donor allo-HCT; no other major differences in outcome.
Rezvani et al. (2011) [42]	Retrospective	Allo-HCT (401)	A ≥0.5 g/dL decrease in serum albumin from baseline until acute GVHD was 69% sensitive and 73% specific predictive for acute GVHD. A ≥0.5 g/dL decrease in serum albumin associated with poorer OS after acute GVHD.
Kharfan-Dabaja et al. (2011) [41]	Retrospective	Allo-HCT (163)	Serum albumin <3 g/dL and Karnofsky Performance Scale score <80 at day +90 independently predicted poorer NRM and OS.
Sivgin et al. (2013) [40]	Retrospective	Allo-HCT (102)	Patients with serum albumin <3.2 g/dL had poorer OS and disease-free survival compared with patients with serum albumin ≥3.2 g/dL.
Dysgeusia and quality of life (QoL)			
Sonis et al. (2001) [2]	Prospective	ASCT and allo-HCT (92)	Measured oral mucositis using OMAS early post-HCT and relationship with post-HCT toxicities. Peak OMAS scores were associated with longer durations of fever, TPN, and opioid use, longer length of hospital stay, and increased risk of day +100 mortality.
Epstein et al. (2002) [3]	Prospective	Allo-HCT (50)	QoL surveys with oral symptom, taste, and smell assessments administered at 3 mo post-HCT. Abnormalities in taste were noted, particularly in sour and bitter tastes. Taste perception was more significantly affected in females compared with males. Increased smell sensitivity was noted.
Campagnaro et al. (2008) [79]	Prospective	ASCT (64)	Evaluation of symptom burden after ASCT for multiple myeloma using the MDASI. High MDASI scores early post-HCT returned to baseline by day +30 in most patients. Women and those with prolonged time to ASCT had higher baseline MDASI scores.

MTX indicates methotrexate; MDASI, M.D. Anderson Symptom Inventory; OMAS, Oral Mucositis Assessment Scale; OS, overall survival; TPN, total parenteral nutrition.

known zinc deficiency, although zinc supplementation is rarely used in practice [86-89]. Most treatment strategies in this area have focused largely on prevention of oropharyngeal mucositis. Attempts to prevent or alleviate oropharyngeal mucositis with such agents as keratinocyte growth factor, free-radical reducers such as amifostine, pentoxifylline, or topical/systemic analgesics have yielded mixed results [90,91]. Three main strategies have shown consistent efficacy in certain patient populations: systemic keratinocyte growth factor in patients undergoing TBI-based myeloablative conditioned HCT, topical cryotherapy in patients receiving high-dose melphalan and ASCT for multiple myeloma, and photomodulation with low-level laser light therapy in various chemotherapy and RT protocols [36,90,92-94]. Each of these strategies has potential advantages and limitations, including variable clinical utility and effectiveness in specific populations, as well as cost considerations [92,95-97]. Good oral hygiene, addressing dental/oral disease and hyposalivation, should be recognized

Table 2
Scoring Systems for Assessing Taste Disturbances

Grade	CTCAE v. 4.0	STTA
0	None	No change in taste acuity from baseline
1	Altered taste with no change in diet	Mild loss of taste acuity, but not inconvenient in daily life
2	Altered taste with change in diet (eg, oral supplements); noxious or unpleasant taste; loss of taste	Moderate loss of taste acuity, sometimes inconvenient in daily life
3	--	Severe loss of taste acuity, frequently inconvenient in daily life
4	--	Almost complete or complete loss of taste acuity

Adapted from Saito et al. [84] and Kluetz et al, [85].

as an important factor in taste management. Potential additional approaches for dysgeusia may include treatment trials of megestrol, cannabinoids, and *Synsepalum dulcificum* (so-called "miracle berry"), which have shown limited evidence of benefit [98]. Studies of these agents in patients undergoing HCT are needed.

Conclusions and Future Directions

Dysgeusia in patients undergoing HCT is a complex syndrome. A better understanding of its etiology and pathobiology, as well as the preventative or therapeutic strategies that could be developed, likely will have a major positive impact on QoL and possibly on other outcomes, such as NRM. As our biological understanding of contributing factors in dysgeusia broadens and deepens, we need innovative and multimodal studies that incorporate our growing knowledge of the interactions between host and microbiota, nutrition and dietary intake, personalized approaches to conditioning regimen administration, immune recovery, and novel preventive strategies, such as photomodulation with low-level laser light therapy. This will open the door to impactful prospective studies that attempt to minimize confounding variables by selecting homogeneous patient populations, diseases, and conditioning platforms. The prospective strategies chosen must include patient-reported outcomes data and should evaluate whether the studied approach is clinically and economically effective. High-quality data from well-defined and carefully selected patient populations may be applicable across HCT platforms and may inform strategies to reduce the incidence, severity, and symptom burden of dysgeusia. Moreover, the information gained through this work also may be relevant in the care of patients undergoing cytotoxic therapy for other malignancies.

ACKNOWLEDGMENTS

Financial disclosure: Philanthropic research support was provided by the Matlin Fund and Sawiris Research Fund.

Conflict of interest statement: J.U.P. receives licensing fees and research support from Seres Therapeutics. The other authors have no conflicts of interest to report.

REFERENCES

1. Epstein JB, Barasch A. Taste disorders in cancer patients: pathogenesis, and approach to assessment and management. *Oral Oncol*. 2010;46:77-81.
2. Sonis ST, Oster G, Fuchs H, et al. Oral mucositis and the clinical and economic outcomes of hematopoietic stem-cell transplantation. *J Clin Oncol*. 2001;19:2201-2205.
3. Epstein JB, Phillips N, Parry J, Epstein MS, Nevill T, Stevenson-Moore P. Quality of life, taste, olfactory and oral function following high-dose chemotherapy and allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant*. 2002;30:785-792.
4. Chaudhry HM, Bruce AJ, Wolf RC, et al. The incidence and severity of oral mucositis among allogeneic hematopoietic stem cell transplantation patients: a systematic review. *Biol Blood Marrow Transplant*. 2016;22:605-616.
5. Harris B, Morjaria SM, Littmann ER, et al. Gut microbiota predict pulmonary infiltrates after allogeneic hematopoietic cell transplantation. *Am J Respir Crit Care Med*. 2016;194:450-463.
6. De Koning C, Nierkens S, Boelens JJ. Strategies before, during, and after hematopoietic cell transplantation to improve T-cell immune-reconstitution. *Blood*. 2016;128:2607-2615.
7. Meier JK, Wolff D, Pavletic S, et al. Oral chronic graft-versus-host disease: report from the International Consensus Conference on clinical practice in cGVHD. *Clin Oral Investig*. 2011;15:127-139.
8. Boer CC, Correa ME, Miranda EC, de Souza CA. Taste disorders and oral evaluation in patients undergoing allogeneic hematopoietic SCT. *Bone Marrow Transplant*. 2010;45:705-711.
9. Majhail NS, Farnia SH, Carpenter PA, et al. Indications for autologous and allogeneic hematopoietic cell transplantation: guidelines from the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2015;21:1863-1869.
10. Muffly L, Pasquini MC, Martens M, et al. Increasing use of allogeneic hematopoietic cell transplantation (HCT) in patients age 70 years and older: a CIBMTR study of trends and outcomes. *Biol Blood Marrow Transplant*. 2016;22:S68-S69.
11. Chaudhari N, Roper SD. The cell biology of taste. *J Cell Biol*. 2010;190:285-296.
12. Nguyen HM, Reyland ME, Barlow LA. Mechanisms of taste bud cell loss after head and neck irradiation. *J Neurosci*. 2012;32:3474-3484.
13. Bermúdez-Rattoni F. Molecular mechanisms of taste-recognition memory. *Nat Rev Neurosci*. 2004;5:209-217.
14. Chen X, Gabitto M, Peng Y, Ryba NJ, Zuker CS. A gustotopic map of taste qualities in the mammalian brain. *Science*. 2011;333:1262-1266.
15. Trivedi BP. Neuroscience: hardwired for taste. *Nature*. 2012;486:S7-S9.
16. Comeau TB, Epstein JB, Migas C. Taste and smell dysfunction in patients receiving chemotherapy: a review of current knowledge. *Support Care Cancer*. 2001;9:575-580.
17. Landis BN, Scheibe M, Weber C, et al. Chemosensory interaction: acquired olfactory impairment is associated with decreased taste function. *J Neurol*. 2010;257:1303-1308.
18. Barasch A, Epstein J. Assessment of taste disorders. *BMJ Best Pract*. 2016. Available at: http://bestpractice.bmj.com/best-practice/monograph/971.html. Accessed June 11, 2017.
19. Epstein JB, Smutzer G, Doty RL. Understanding the impact of taste changes in oncology care. *Support Care Cancer*. 2016;24:1917-1931.
20. IJpma I, Renken RJ, Ter Horst GJ, Reyners AK. Metallic taste in cancer patients treated with chemotherapy. *Cancer Treat Rev*. 2015;41:179-186.
21. Bressan V, Stevanin S, Bianchi M, Aleo G, Bagnasco A, Sasso L. The effects of swallowing disorders, dysgeusia, oral mucositis and xerostomia on nutritional status, oral intake and weight loss in head and neck cancer patients: a systematic review. *Cancer Treat Rev*. 2016;45:105-119.
22. Buglione M, Cavagnini R, Di Rosario F, et al. Oral toxicity management in head and neck cancer patients treated with chemotherapy and radiation: xerostomia and trismus (Part 2). Literature review and consensus statement. *Crit Rev Oncol Hematol*. 2016;102:47-54.
23. Jensen SB, Pedersen AM, Vissink A, et al. A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: prevalence, severity and impact on quality of life. *Support Care Cancer*. 2010;18:1039-1060.
24. Bergdahl M, Bergdahl J. Perceived taste disturbance in adults: prevalence and association with oral and psychological factors and medication. *Clin Oral Investig*. 2002;6:145-149.
25. Ciancio SG. Medications' impact on oral health. *J Am Dent Assoc*. 2004;135:1440-1448.
26. Hovan AJ, Williams PM, Stevenson-Moore P, et al. A systematic review of dysgeusia induced by cancer therapies. *Support Care Cancer*. 2010;18:1081-1087.
27. Naik BS, Shetty N, Maben EV. Drug-induced taste disorders. *Eur J Intern Med*. 2010;21:240-243.

28. Vigarios E, Epstein JB, Sibaud V. Oral mucosal changes induced by anticancer targeted therapies and immune checkpoint inhibitors. *Support Care Cancer*. 2017;25:1713-1739.
29. Wang T, Glendinning J, Grushka M, Hummel T, Mansfield K. Drug-induced taste disorders in clinical practice and preclinical safety evaluation. *Toxicol Sci*. 2017;156:315-324.
30. Marinone MG, Rizzoni D, Ferremi P, Rossi G, Izzi T Brusotti C. Late taste disorders in bone marrow transplantation: clinical evaluation with taste solutions in autologous and allogeneic bone marrow recipients. *Haematologica*. 1991;76:519-522.
31. Mattsson T, Arvidson K, Heimdahl A, Ljungman P, Dahllof G Ringdén O. Alterations in taste acuity associated with allogeneic bone marrow transplantation. *J Oral Pathol Med*. 1992;21:33-37.
32. Pasquini MC, Wang Z. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR summary slides, 2013. Available at: https://www.cibmtr.org/ReferenceCenter/SlidesReports/SummarySlides/pages/index.aspx. Accessed November 6, 2017.
33. Chen YB, Lane AA, Logan B, et al. Impact of conditioning regimen on outcomes for patients with lymphoma undergoing high-dose therapy with autologous hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2015;21:1046-1053.
34. Okada N, Hanafusa T, Abe S, et al. Evaluation of the risk factors associated with high-dose chemotherapy-induced dysgeusia in patients undergoing autologous hematopoietic stem cell transplantation: possible usefulness of cryotherapy in dysgeusia prevention. *Support Care Cancer*. 2016;24:3979-3985.
35. Cutler C, Li S, Kim HT, et al. Mucositis after allogeneic hematopoietic stem cell transplantation: a cohort study of methotrexate- and non-methotrexate-containing graft-versus-host disease prophylaxis regimens. *Biol Blood Marrow Transplant*. 2005;11:383-388.
36. Goldberg JD, Zheng J, Castro-Malaspina H, et al. Palifermin is efficacious in recipients of TBI-based but not chemotherapy-based allogeneic hematopoietic stem cell transplants. *Bone Marrow Transplant*. 2013;48:99-104.
37. Wang XS, Shi Q, Williams LA, et al. Inflammatory cytokines are associated with the development of symptom burden in patients with NSCLC undergoing concurrent chemoradiation therapy. *Brain Behav Immun*. 2010;24:968-974.
38. Malone FR, Leisenring WM, Storer BE, et al. Prolonged anorexia and elevated plasma cytokine levels following myeloablative allogeneic hematopoietic cell transplant. *Bone Marrow Transplant*. 2007;40:765-772.
39. Mattsson J, Westin S, Edlund S, Remberger M. Poor oral nutrition after allogeneic stem cell transplantation correlates significantly with severe graft-versus-host disease. *Bone Marrow Transplant*. 2006;38:629-633.
40. Sivgin S, Baldane S, Ozenmis T, et al. The impact of pretransplant hypoalbuminemia on survival in patients with leukemia who underwent allogeneic hematopoietic stem cell transplantation (alloHSCT): a nutritional problem? *Transplant Proc*. 2013;45:3371-3374.
41. Kharfan-Dabaja MA, Chavez JC, Yu D, et al. Severe hypoalbuminemia at day 90 predicts worse nonrelapse mortality and overall survival after allogeneic hematopoietic stem cell transplantation for acute myelogenous leukemia and myelodysplastic syndrome. *Biol Blood Marrow Transplant*. 2011;17:384-393.
42. Rezvani AR, Storer BE, Storb RF, et al. Decreased serum albumin as a biomarker for severe acute graft-versus-host disease after reduced-intensity allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2011;17:1594-1601.
43. Rondon G, Saliba RM, Chen J, et al. Fluid overload as new toxicity category has a strong impact on non relapse mortality and survival in allogeneic hematopoietic stem cell transplantation. *Blood*. 2015;126:4321.
44. O'Connor ME, Prowle JR. Fluid overload. *Crit Care Clin*. 2015;31:803-821.
45. Mitchell KH, Carlbom D, Caldwell E, Leary PJ, Himmelfarb J, Hough CL. Volume overload: prevalence, risk factors, and functional outcome in survivors of septic shock. *Ann Am Thorac Soc*. 2015;12:1837-1844.
46. Baumgartner A, Bargetzi A, Zueger N, et al. Revisiting nutritional support for allogeneic hematologic stem cell transplantation—a systematic review. *Bone Marrow Transplant*. 2017;52:506-513.
47. Navarro WH, Agovi MA, Logan BR, et al. Obesity does not preclude safe and effective myeloablative hematopoietic cell transplantation (HCT) for acute myeloid leukemia (AML) in adults. *Biol Blood Marrow Transplant*. 2010;16:1442-1450.
48. Armenian SH, Horak D, Scott JM, et al. Cardiovascular function in long-term hematopoietic cell transplantation survivors. *Biol Blood Marrow Transplant*. 2017;23:700-705.
49. August DA, Huhmann MB. ASPEN clinical guidelines: nutrition support therapy during adult anticancer treatment and in hematopoietic cell transplantation. *JPEN J Parenter Enteral Nutr*. 2009;33:472-500.
50. Seguy D, Berthon C, Micol JB, et al. Enteral feeding and early outcomes of patients undergoing allogeneic stem cell transplantation following myeloablative conditioning. *Transplantation*. 2006;82:835-839.
51. Guièze R, Lemal R, Cabrespine A, et al. Enteral versus parenteral nutritional support in allogeneic haematopoietic stem-cell transplantation. *Clin Nutr*. 2014;33:533-538.
52. Lemal R, Cabrespine A, Pereira B, et al. Could enteral nutrition improve the outcome of patients with haematological malignancies undergoing allogeneic haematopoietic stem cell transplantation? A study protocol for a randomized controlled trial (the NEPHA study). *Trials*. 2015;16:136.
53. Sicotte M, Langlois EV, Aho J, Ziegler D, Zunzunegui MV. Association between nutritional status and the immune response in HIV$^+$ patients under HAART: protocol for a systematic review. *Syst Rev*. 2014;3:9.
54. van den Brink MRM, Velardi E, Perales MA. Immune reconstitution following stem cell transplantation. *Hematol Am Soc Hematol Educ Progr*. 2015;2015:215-219.
55. Savino W. The thymus gland is a target in malnutrition. *Eur J Clin Nutr*. 2002;56(Suppl 3):S46-S49.
56. Lynch HE, Goldberg GL, Chidgey A, Van den Brink MR, Boyd R, Sempowski GD. Thymic involution and immune reconstitution. *Trends Immunol*. 2009;30:366-373.
57. Savino W, Dardenne M. Nutritional imbalances and infections affect the thymus: consequences on T-cell-mediated immune responses. *Proc Nutr Soc*. 2010;69:636-643.
58. Gruver AL, Hudson LL, Sempowski GD. Immunosenescence of ageing. *J Pathol*. 2007;211:144-156.
59. Heyland DK, Novak F, Drover JW, Jain M, Su X, Suchner U. Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. *JAMA*. 2001;286:944-953.
60. Montejo JC, Zarazaga A, López-Martínez J, et al. Immunonutrition in the intensive care unit: a systematic review and consensus statement. *Clin Nutr*. 2003;22:221-233.
61. Heyland D, Muscedere J, Wischmeyer PE, et al. A randomized trial of glutamine and antioxidants in critically ill patients. *N Engl J Med*. 2013;368:1489-1497.
62. van Niekerk G, Isaacs AW, Nell T, Engelbrecht AM. Sickness-associated anorexia: mother nature's idea of immunonutrition? *Mediators Inflamm*. 2016;2016:8071539.
63. Clemente JC, Ursell LK, Parfrey LW, Knight R. The impact of the gut microbiota on human health: an integrative view. *Cell*. 2012;148:1258-1270.
64. Paulos CM, Wrzesinski C, Kaiser A, et al. Microbial translocation augments the function of adoptively transferred self/tumor-specific CD8$^+$ T cells via TLR4 signaling. *J Clin Invest*. 2007;117:2197-2204.
65. Peled JU, Jenq RR, Holler E, van den Brink MR. Role of gut flora after bone marrow transplantation. *Nat Microbiol*. 2016;1:16036.
66. Taur Y, Jenq RR, Perales MA, et al. The effects of intestinal tract bacterial diversity on mortality following allogeneic hematopoietic stem cell transplantation. *Blood*. 2014;124:1174-1182.
67. Jenq RR, Taur Y, Devlin SM, et al. Intestinal blautia is associated with reduced death from graft-versus-host disease. *Biol Blood Marrow Transplant*. 2015;21:1373-1383.
68. Shono Y, Docampo MD, Peled JU, et al. Increased GVHD-related mortality with broad-spectrum antibiotic use after allogeneic hematopoietic stem cell transplantation in human patients and mice. *Sci Transl Med*. 2016;8:339ra71.
69. Peled JU, Hanash AM, Jenq RR. Role of the intestinal mucosa in acute gastrointestinal GVHD. *Hematol Am Soc Hematol Educ Program*. 2016;2016:119-127.
70. Lee YJ, Arguello EP, Jenq RR, et al. Protective factors in the intestinal microbiome against clostridium difficile infection in recipients of allogeneic hematopoietic stem cell transplantation. *J Infect Dis*. 2017;215:1117-1123.
71. David LA, Maurice CF, Carmody RN, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature*. 2014;505:559-563.
72. Lyte M, Fodor AA, Chapman CD, et al. Gut microbiota and a selectively bred taste phenotype: a novel model of microbiome-behavior relationships. *Psychosom Med*. 2016;78:610-619.
73. Littmann E, Ling L, Morjaria S, et al. Serial changes in oral and respiratory microbiota in patients undergoing hematopoietic stem cell transplantation: a pilot study. *Am J Respir Crit Care Med*. 2015;191:A1787. Available at: http://www.atsjournals.org/doi/pdf/10.1164/ajrccm-conference.2015.191.1_MeetingAbstracts.A1787. Accessed July 23, 2017.
74. Vanhoecke B, De Ryck T, Stringer A, Van de Wiele T, Keefe D. Microbiota and their role in the pathogenesis of oral mucositis. *Oral Dis*. 2015;21:17-30.
75. Vasconcelos RM, Sanfilippo N, Paster BJ, et al. Host-microbiome cross-talk in oral mucositis. *J Dent Res*. 2016;95:725-733.
76. Segata N, Haake S, Mannon P, et al. Composition of the adult digestive tract bacterial microbiome based on seven mouth surfaces, tonsils, throat and stool samples. *Genome Biol*. 2012;13:R42.
77. Napeñas JJ, Brennan MT, Bahrani-Mougeot FK, Fox PC, Lockhart PB. Relationship between mucositis and changes in oral microflora during cancer chemotherapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2007;103:48-59.
78. Laheij AM, de Soet JJ, von dem Borne PA, et al. Oral bacteria and yeasts in relationship to oral ulcerations in hematopoietic stem cell transplant recipients. *Support Care Cancer*. 2012;20:3231-3240.
79. Campagnaro E, Saliba R, Giralt S, et al. Symptom burden after autologous stem cell transplantation for multiple myeloma. *Cancer*. 2008;112:1617-1624.

80. Cleeland CS, Bennett GJ, Dantzer R, et al. Are the symptoms of cancer and cancer treatment due to a shared biologic mechanism? A cytokine-immunologic model of cancer symptoms. *Cancer*. 2003;97:2919-2925.
81. Cleeland CS. Symptom burden: multiple symptoms and their impact as patient-reported outcomes. *J Natl Cancer Inst Monogr*. 2007;37:16-21.
82. Deems DA, Doty RL, Settle RG, et al. Smell and taste disorders, a study of 750 patients from the University of Pennsylvania Smell and Taste Center. *Arch Otolaryngol Head Neck Surg*. 1991;117:519-528.
83. Bergstrom J. Mechanisms of uremic suppression of appetite. *J Ren Nutr*. 1999;9:129-132.
84. Saito T, Miyake M, Kawamori J, et al. Buccal mucosal cancer patient who failed to recover taste acuity after partial oral cavity irradiation. *Radiat Med*. 2002;20:257-260.
85. Kluetz PG, Chingos DT, Basch EM, Mitchell SA. Patient-reported outcomes in cancer clinical trials: measuring symptomatic adverse events with the National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *Am Soc Clin Oncol Educ Book*. 2016;35:67-73.
86. Henkin RI, Schecter PJ, Friedewald WT, Demets DL, Raff M. A double blind study of the effects of zinc sulfate on taste and smell dysfunction. *Am J Med Sci*. 1976;272:285-299.
87. Sakai F, Yoshida S, Endo S, Tomita H. Double-blind, placebo-controlled trial of zinc picolinate for taste disorders. *Acta Otolaryngol Suppl*. 2002;546:129-133.
88. Heckmann SM, Hujoel P, Habiger S, et al. Zinc gluconate in the treatment of dysgeusia: a randomized clinical trial. *J Dent Res*. 2005;84:35-38.
89. Lyckholm L, Heddinger SP, Parker G, et al. A randomized, placebo controlled trial of oral zinc for chemotherapy-related taste and smell disorders. *J Pain Palliat Care Pharmacother*. 2012;26:111-114.
90. Raber-Durlacher JE, Barasch A, Peterson DE, Lalla RV, Schubert MM, Fibbe WE. Oral complications and management considerations in patients treated with high-dose chemotherapy. *Support Cancer Ther*. 2004;1:219-229.
91. Nicolatou-Galitis O, Sarri T, Bowen J, et al. Systematic review of amifostine for the management of oral mucositis in cancer patients. *Support Care Cancer*. 2013;21:357-364.
92. Spielberger R, Stiff P, Bensinger W, et al. Palifermin for oral mucositis after intensive therapy for hematologic cancers. *N Engl J Med*. 2004;351:2590-2598.
93. Bjordal JM, Bensadoun RJ, Tunèr J, Frigo L, Gjerde K, Lopes-Martins RA. A systematic review with meta-analysis of the effect of low-level laser therapy (LLLT) in cancer therapy-induced oral mucositis. *Support Care Cancer*. 2011;19:1069-1077.
94. Peterson DE, Ohrn K, Bowen J, et al. Systematic review of oral cryotherapy for management of oral mucositis caused by cancer therapy. *Support Care Cancer*. 2013;21:327-332.
95. Nooka AK, Johnson HR, Kaufman JL, et al. Pharmacoeconomic analysis of palifermin to prevent mucositis among patients undergoing autologous hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2014;20:852-857.
96. Herbers AH, van der Velden WJ, de Haan AF, Donnelly JP, Blijlevens NM. Impact of palifermin on intestinal mucositis of HSCT recipients after BEAM. *Bone Marrow Transplant*. 2014;49:8-10.
97. Bezinelli LM, de Paula Eduardo F, da Graça Lopes RM, et al. Cost-effectiveness of the introduction of specialized oral care with laser therapy in hematopoietic stem cell transplantation. *Hematol Oncol*. 2014;32:31-39.
98. Thorne T, Olson K, Wismer W. A state-of-the-art review of the management and treatment of taste and smell alterations in adult oncology patients. *Support Care Cancer*. 2015;23:2843-2851.