

Clinical approach in the management of oral chronic graft-versus-host disease (cGVHD) in a series of specialized medical centers

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Abstract

Background The oral cavity is frequently affected in chronic graft-versus-host disease (cGVHD), with variable clinical presentations. The literature on the effective management of patients suffering from oral cGVHD is limited.

Objective The objective of this study was to assess the clinical approaches used in the diagnosis and treatment of cGVHD in a group of health-care providers specialized in the oral care of oncology patients. The secondary objective was to assess the level of implementation of the

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National Institutes of Health (NIH) guidelines for cGVHD patients.

Methods One hundred twenty questionnaires were sent to the members of the Oral Care Study Group (OCSG) of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). The questionnaire included 50 questions about the responder's demographics, level of exposure to cGVHD patients, diagnostic and evaluation methods in their practice, preferred treatment strategies for mucosal and salivary gland involvement, and preventive measures. **Results** Twelve responders, representing 12 sites, stated that they treat oral cGVHD patients on a regular basis. This fraction of responders was confirmed by another online survey. Eleven out of the 12 providers were dentists. Seventy-five percent of the providers did not use biopsy in order to diagnose oral cGVHD. The NIH scale for the clinical assessment was used sporadically. The first-line topical treatment for oral mucosal cGVHD was predominantly steroids (91.7 %), and the second preferred treatment was tacrolimus (41.7 %). The preferred treatment for hyposalivation was pilocarpine (41.7 %). The recommended frequency of oral cancer screening varied; half of the providers suggest a follow-up every 6 months.

Conclusions The responses described the common practices for oral cGVHD in several specialized centers across the world. The choice of topical treatments was influenced by the availability of medications in the provider's country.

Keywords Oral chronic graft-versus-host disease · NIH scale · Oral care · Topical treatment · Oral mucosa · Salivary glands · Oral cancer

Introduction

Chronic graft-versus-host disease (cGVHD) is a major complication of allogeneic hematopoietic stem cell transplantation (HSCT). Graft-versus-host disease is an alloimmune inflammatory process, which results from a donor–origin cellular response directed against host tissues [1, 2]. cGVHD is known

to cause damage to the oral mucosa, the salivary glands, and the perioral musculoskeletal tissues [3–7]. Historically, cGVHD was diagnosed 100 days post-HSCT; however, oral cGVHD is now diagnosed based on clinical presentation regardless of onset time [3, 8].

The clinical presentation includes oral lesions common in autoimmune diseases, such as lichenoid, erythematous, and ulcerative mucosal lesions [9]. Salivary gland hypofunction, xerostomia, loss of range of motion of soft tissues, decreased mouth opening, and superficial mucoceles are also common in oral cGVHD [5, 10].

Although cGVHD is a systemic disease, topical oral treatments have an important role particularly when the only tissues involved are in the oral cavity or when these lesions do not respond to systemic treatments for cGVHD. Systemic treatments are usually given when more than two organs are involved or any organ score of 2 or more [11], which point at the role of topical treatment in cases when the oral tissues are the only organ involved or is the most symptomatic site. In such cases, local therapy allows improved control without increasing systemic therapy. Oral topical treatments aim to relieve symptoms, maintain mucosal integrity, alleviate hyposalivation and to prevent secondary damage to the teeth and secondary oral infections. An important aspect of oral cGVHD management is screening for secondary oral cancer as this population has an increased risk, particularly for squamous cell carcinoma [12–15].

In the early 1990s, the oral mucosal index (OMI) was introduced to help quantify the type and severity of oral mucosal changes [16]. In 2005–2006, the National Institutes of Health (NIH) published a series of position papers suggesting diagnostic criteria as well as a system to characterize and grade the level of oral cGVHD activity [3, 8, 12]. An international forum under the auspice of the German–Austrian–Swiss working group on bone marrow and blood stem cell transplantation [17] published guidelines for the diagnosis, grading, and management of oral cGVHD based on a systematic review that ranked the published scientific evidence [12, 17]. Similarly, the British society for bone marrow transplantation published treatment recommendations [18]. The evidence used to develop the position paper and guidelines relied primarily on case series publications and expert opinion.

Conducting well-designed clinical trials for the development of effective topical treatment is challenging, and currently, research reports are scarce, and most treatment strategies and intervention protocols in cGVHD are based on observational studies and on expert consensus [12]. Accordingly, the primary aim of this survey was to define the most common clinical approaches to patients with oral cGVHD. Furthermore, considering that the publications of the NIH working group form the basis of the treatment of cGVHD patients, we evaluated whether these guidelines, including the assessment tools, have been integrated into common practice. Therefore,

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the secondary objective of this study was to assess the use of the NIH scales for diagnosis and for assessment of oral cGVHD activity.

Methods

Identification of medical centers treating oral cGVHD

Members of the Oral Care Study Group (OCSG) of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) were the target population of the survey, who represent a multinational multidisciplinary group of medical and dental professionals that focus on supportive care in oral oncology.

An electronic questionnaire was prepared. The first question assessed the level of exposure to oral cGVHD patients. This question was used to identify centers with clinical services oriented at oral cGVHD. The questionnaire was distributed electronically by the study group chair along with a cover letter from the principal investigator (PI). Two rounds of distribution were performed. In order to maintain confidentiality, the responses were returned directly to the PI (according to the directions of the Institutional Review Board). As a confirmatory tool, a single yes/no question was submitted through an online survey website (www.surveymonkey.com).

Collecting data on the standards of management of oral cGVHD

The structured survey contained questions about the responder's demographics, whether or not they treat oral cGVHD, evaluation tools, diagnostic aids, topical treatments, and preventive measures. Data were tabulated in Microsoft Excel software, and a descriptive analysis was performed. This study was approved by the Institutional Review Board of the University of Rochester.

Results

Identifying centers with a clinical service focused on oral cGVHD patients

Of the 120 questionnaires originally sent to the OCSG members, 17 (14.2 %) members responded, and 12 (70.6 % of the responders) stated that they treat oral cGVHD patients on a regular basis. Eighteen (15.0 %) members responded positively to the single confirmatory online question regarding regular encounters with oral cGVHD patients. Therefore, both submissions reached a similar proportion of responders with a focused clinical service for oral cGVHD. Therefore, the full-length questionnaire obtained from the 17 providers was used for the analysis.

Demographics of responders

The average age of the providers who were treating oral cGVHD was 48.2 ± 9.7 years old. Six (50 %) of the providers practice in the USA, and 6 (50 %) practice in Europe. Eleven out of 12 (91.7 %) providers were dentists. Table 1 includes demographic data.

Diagnosis and evaluation of oral cGVHD

Table 2 shows the diagnostic and evaluation tools used by the health-care providers. A diagnosis based on the NIH definition is used in 3 out of 12 (25 %) centers. Biopsy was not required for diagnosis of oral cGVHD by most of the clinics (66.7 %). Eight out of 12 (66.7 %) health-care providers used a standard assessment tool to evaluate patients' symptoms. The visual analog scale (VAS) for pain was the most commonly used scale for pain assessment [12, 19]. Half of the providers used a standard assessment tool to evaluate clinical signs. The NIH scale for grading response and the mucosal rating index were used at similar rates (41.7–50 %), with slight

Table 1 Demographic data of oral health-care providers

		All responses	Responders experienced with oral cGVHD
Age (years)		50±10.7	48.2±9.8
Geography	US/Europe/Canada	8/8/1	6/6/0
Profession	Dentist/physician	15/2	11/1
Type of institute/clinic	Cancer center	6	5
	Dental school	4	3
	Dental clinic at hospital	3	1
	General hospital	3	3
	Private OM clinic	1	0

cGVHD chronic graft-versus-host disease, OM oral medicine, US United States

Table 2 Method of diagnosis and evaluation tools

	Optional answer	Number of sites (%)
Diagnosis		
NIH definition for diagnosis	Yes	5 (41.7 %)
Biopsy for cGVHD diagnosis	Almost none	8 (66.7 %)
	In 25 %	1 (8.3 %)
	In 50 %	2 (16.7 %)
	Almost all	1 (8.3 %)
Diagnosis—hyposalivation	1. Sialometry	8 (75 %)
	2. Saliva appearance (mucoïd)	7 (58.3 %)
	3. Appearance of lingual pool	5 (41.7 %)
	4. Other ^a	1 (8.3 %)
Evaluation tool		
Standard—subjective	Yes	8 (75 %)
	1. VAS for pain	7 (58.3 %)
	2. NIH subjective ladder	4 (33 %)
	3. WHO for pain	2 (16.7 %)
Standard—objective	Yes	6 (50 %)
	1. Mucosal rating index	6 (50 %)
	2. NIH for grading response	5 (41.7 %)
	3. Other ^b	1 (8.3 %)

cGVHD chronic graft-versus-host disease, NIH National Institutes of Health, VAS visual analog scale, WHO World Health Organization

^aLack of expression of saliva from the salivary duct and based on the thickness and clarity of the saliva

^bOMRS (oral mucositis rating scale)

preference for the mucosal rating index. Regarding the salivary gland cGVHD, 75 % of providers used sialometry to diagnose hyposalivation; however, only 50 % used sialometry routinely for every patient. Seven out of 12 (58.3 %) providers assessed saliva appearance (viscous/mucoïd consistency), and five (41.7 %) providers evaluated hyposalivation by the appearance of a lingual pool of saliva.

Topical interventions for mucosal cGVHD

Based on the responses, topical treatments for mucosal cGVHD were used under three circumstances: (a) when oral cGVHD is resistant to systemic treatment (58.3 %), (b) when oral cGVHD is the only site of involvement (58.3 %), and (c) concomitantly with systemic treatment as first-line therapy (41.7 %). One (8.3 %) health-care provider specified that pain is a primary indication for topical treatment. Table 3 shows the health-care providers' preferred treatment options. The first-line topical treatment for mucosal cGVHD was predominantly steroids (91.7 %), with tacrolimus the second preferred topical treatment (41.7 %). Topical steroids were also commonly used as a second-line treatment. Topical anesthetics were used as palliative treatments for oral mucosal cGVHD in 91.7 %, whereas systemic narcotics were used

by 8.3 %. The preferred treatment for hyposalivation was pilocarpine (41.7 %). Cevimeline was rarely used for salivary gland-involved cGVHD. As palliative treatment, saliva substitutes were used by half of the responders, and 25 % recommended frequent water sips for palliation.

Routine dental care and oral surveillance

Table 4 shows the approach to routine dental care and oral tissue surveillance, including the preventive protocol. Thirty percent of the providers recommended a 3- or 6-month recall to assess the dental status. Ninety percent of practitioners recommended routine fluoride use; fluoride regimens were directly advised to patients by the specialized oral care providers or provided by their own treating dentist. Almost all respondents supported the establishment of an oral cancer screening protocol (91.7 %). The recommended frequency of oral cancer screening varied with half of the providers suggesting a 6-month frequency. Sixty-seven percent of practitioners informed their patients about the risk of oral cancer. Preventive protocols were utilized by 50 % of the responders. Specifically, antifungal prophylaxis was recommended for the prevention of oral candidiasis in 33 % of the response, indicated following a recurrence of clinical oral candidiasis.

Table 3 Preferred oral mucosal and salivary gland interventions

	Intervention	Number of sites (%)
Oral mucosal cGVHD interventions		
Preferred topical first line	Steroids	11 (91.7 %)
	N/R ^a	1 (8.3 %)
Preferred topical second line	Tacrolimus	5 (41.7 %)
	Steroids	3 (25 %)
	Cyclosporine	1 (8.3 %)
	Azathioprine	1 (8.3 %)
	Phototherapy ^b	1 (8.3 %)
	N/R ^a	1 (8.3 %)
Palliation	Topical anesthetic	11 (91.7 %)
	Systemic narcotics	1 (8.3 %)
	Laser (soft)	0
Salivary cGVHD intervention		
Preferred first line	Pilocarpine	5 (41.7 %)
	Cevimeline	1 (8.3 %)
	Other ^c	6 (50 %)
Preferred second line	Cevimeline	5 (41.7 %)
	Pilocarpine	3 (25 %)
	Others ^d	3 (25 %)
Palliation first line	Saliva substitute	8 (66.7 %)
	Sugar-free gum/candy	1 (8.3 %)
	Frequent water sips	2 (16.7 %)
	Other	1 (8.3 %)
Palliation second line	Saliva substitute	4 (33.3 %)
	Frequent water sips	3 (25 %)
	Sugar-free gum/candy	2 (16.7 %)
	Other ^{a,e}	3 (25 %)

cGVHD chronic graft-versus-host disease, N/R not reported

^a Not reported/not specified

^b Ultraviolet B (UVB)

^c Topical salivary stimulants and topical moisture enhancers

^d Bethanechol, electrostimulator

^e Pilocarpine, cevimeline

Discussion

The primary objective of this study was to determine the common treatment approaches for patients with oral cGVHD. A survey was developed to identify centers with specialized clinics for oral cGVHD. It was distributed through the OCSG of MASCC/ISOO to gather information from an international focus group regarding the management of oral cGVHD. The rationale was that the collective treatment approach from the survey will supplement the scarce scientific evidence for medical and palliative management.

The survey captured a small selective group of professionals who manage oral cGVHD based on the participants self identification. The small size of the group may represent a small number of medical professionals dedicated to this topic or minimal exposure to severe cases of oral cGVHD or reflect the small number of centers performing HSCT and managing oral cGVHD.

Most of the responders stated that they do not require a biopsy to diagnose oral cGVHD. This complies with the NIH concept that the clinical observation of specific oral lesions (e.g., lichenoid lesion or sclerosis) is sufficient for the diagnosis of oral cGVHD [8]. According to the NIH consensus statement, oral cGVHD may be diagnosed without an oral biopsy if the oral manifestation is distinctive for cGVHD and systemic cGVHD is diagnosed based on other tests.

The study found that the preferred topical agents for the management of mucosal cGVHD are steroids. The literature shows that the use of high-potency corticosteroids is beneficial to patients presenting with mucosal symptoms; however, it may increase the risk of fungal infection [12, 20–23]. Therefore, one may anticipate a concomitant administration of topical antifungal with the topical steroids particularly in the presence of comorbid risk factors such as hyposalivation and diabetes. In this study, although 91.7 % preferred steroids as the primary topical treatment for the management of mucosal cGVHD, only 33.3 % prescribed antifungal medication prophylactically whereas others may wait for evidence of secondary candidiasis prior to antifungal treatment. One possible explanation for the infrequent use of antifungal preventive therapy is that continuous antifungal prophylaxis is only given to patients with additional risk factors for oral candidiasis, such as a history of oral candidiasis during previous courses of topical steroids. Additional possible explanation for the infrequent use of topical nystatin or miconazole antifungal preventive therapy may be due to high sucrose content and caries risk. It is noteworthy that other less cariogenic antifungals are available and if topical sugar-containing nystatin is chosen, accompanying cautions to minimize the tendency for caries are recommended (fluoride use, good oral hygiene, and frequent dental recalls).

The second preferred treatment for mucosal lesions was tacrolimus (41.7 %). The effect of this immunosuppressive is caused by the inhibition of T-helper lymphocyte activation [24]. Previous reports demonstrated that topical treatment with tacrolimus may be helpful, especially in combination with a topical steroid [25–28]. However, most studies supporting the topical use of tacrolimus for oral cGVHD are case reports or representing a mixed topical effect with another topical therapy; thus, more controlled studies are warranted. Given a “black box warning” regarding the risk of lymphomas and other malignancies in patients receiving

Table 4 Dental routine and oral surveillance

		Number of sites (%)
Dental/oral routine		
Dental recall frequency	Every 3 months	4 (33.3 %)
	Every 6 months	4 (33.3 %)
	Tailored according to patient's need	3 (25 %)
	Every year	0
	N/R ^a	1 (8.3 %)
Fluoride	Yes	10 (83.3 %)
	No	1 (8.3 %)
	N/R ^a	1 (8.3 %)
Oral cancer screening		
Oral cancer screening	Yes	11 (91.7 %)
	No	1 (8.3 %)
Oral cancer screening frequency	Once every 6 months	5 (41.7 %)
	Once every 12 months	1 (8.3 %)
	Other ^b	6 (50 %)
Patient education about cancer	Yes	8 (66.7 %)
	No	4 (33.3 %)
Preventive protocol		
Utilize preventive protocol	Yes—caries/periodontal prevention	6 (50 %)
	Yes—antifungal	4 (33.3 %)
	No	6 (50 %)
Antifungal prophylaxis	In Frequently candidiasis recurring	10 (83.3 %)
	For all oral cGVHD patients	2 (16.7 %)
	Based on laboratory results for <i>Candida spp.</i>	0
	Based on signs of hyposalivation	0

cGVHD chronic graft-versus-host disease, N/R not reported

^a Not reported/not specified

^b Depends on the activity of cGVHD, at each dental evaluation, or not specified

immunosuppressants, further evaluation and follow-up is needed [25, 26, 29].

The preferred palliation for mucosal cGVHD-associated pain was local anesthetics followed by systemic narcotics. Considering the limited analgesic potential of topical local anesthetics on one hand and the addictive risk associated with narcotics on the other hand, nonnarcotic treatment options should be explored. Examples of potential methods include coating agents, less popular topical anesthetics (e.g., dyclonine), topical analgesics (e.g., doxepin), nonsteroidal anti-inflammatory drugs, or low-level laser therapy [17, 30]. For severe oral pain, topical application of opioids may reduce systemic adverse effects of systemic opioids [31].

For salivary gland involvement, sialogogues are preferred by most clinicians. Pilocarpine has been prescribed for the management of xerostomia for over three decades, mostly for patients diagnosed with Sjogren syndrome and in patients post-radiotherapy to the head and neck. A few studies proposed its use for oral cGVHD [32–34]. Cevimeline was introduced later, and its efficacy was reported

in a series of oral cGVHD patients [35]. However, pilocarpine and cevimeline are not approved for the treatment of xerostomia in all countries. This lack of availability may have had an impact on the results of the study, as most of the sites in this survey did not report using it as the preferred first-line treatment for xerostomia. While clinically significant adverse effects from using either pilocarpine or cevimeline are uncommon, the clinician should be aware that gastric fluid secretion may be increased in patients with gastrointestinal cGVHD and that reactive airway and obstructive pulmonary disease may develop in cGVHD patients; both complications may be exacerbated by these sialogogues. As hyposalivation increases so does the risk of dental caries [36], and 83.3 % of the providers stated the inclusion of fluoride applications in their routine dental preventive protocol.

The study indicated that the vast majority of the clinicians perform an evaluation for signs of oral cancer. The frequency of evaluation ranged between once a year and more than three

times a year. This is in accordance with the collective opinion obtained through a survey of Diplomats of the American Academy of Oral Medicine regarding the frequency of follow-up for potentially malignant diseases [37]. In the latter survey, a follow-up frequency of more than twice a year was recommended for red lesions, lesions with histologically confirmed dysplasia or both. Although that survey was not focused on oral cGVHD, it seems that the same principle applies. Oral squamous cell carcinoma in cGVHD patients was reported to be more aggressive and to develop on average 8 years post-HSCT [13, 38–42]. Sixty-seven percent of the participants educate the patients about the high risk for oral cancer. Practitioners managing the care of these patients need the appropriate communication skills to inform the patients about this risk while avoiding unnecessary amplification of the patient's concerns.

A secondary objective of this study was to assess the level of implementation of various diagnostic and assessment aids published previously for cGVHD. Forty-two percent of sites adopted the NIH approach for the diagnosis of oral cGVHD. The 2005 publication by the NIH working force of the new tool for the assessment of oral cGVHD was an important addition to the armamentarium for the clinicians working in this field [8]. The goal was that this scale would be used by the entire transplant team. The NIH scale for oral cGVHD was validated in several studies, and some flaws were noted [43–45]. The results of the present study showed that the majority of clinics used a standard tool to evaluate symptoms, mostly VAS for pain. However, there is no common practice for the evaluation of the clinical signs of oral cGVHD. The NIH scale for grading response is not used routinely by most responders. This result may be explained by the fact that the NIH scale was developed as a research tool, not necessarily to be used in all clinical encounters. Even though the scale was designed to for the use of multiple medical disciplines, its application is time-consuming and requires training and experience to use it appropriately. The use of a standard assessment tool in the clinical setting will enable standard data collection across medical centers and will allow conclusions regarding the management to be made. The 2014 NIH-NCI conference on cGVHD identified the need to modify the NIH scale for oral cGVHD. Hopefully, the future NIH scale for oral cGVHD will have a significant role in clinical practice.

A limitation of this study is the underrepresentation of the medical providers treating this condition. Although the survey addressed a large heterogeneous group of health-care providers from the discipline of oncology, there were fewer physicians among the responders than expected. Yet, it may represent the reality that complex treatment for oral cGVHD is delivered mostly by specialist/experienced oral care health providers.

In summary, the responses portrayed the common approach to management for oral cGVHD in several specialized centers across the globe. The potential for broad application of

the NIH scale for activity assessment laid the foundation for an assembly of a professional network of clinics focused on oral cGVHD intending to collect evidence-based quality data.

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The corresponding author has full control of all primary data and agrees to allow the journal to review these data if requested.

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