Oral chronic graft-versus-host disease is a frequent complication of allogeneic hematopoietic stem cell transplantation, contributing to patient morbidity and mortality. Although an optimal treatment is not available, several systemic and topical or local therapies have shown efficacy in treating the disease. New therapies are being tested through clinical trials. This article examines the efficacy and safety of reported treatment modalities studied from 2006–2012. Nurses will encounter patients with oral chronic graft-versus-host disease suffering from pain, discomfort, and a decreased quality of life. Knowledge of new therapies found to be effective in managing these symptoms is imperative. Nurses play a key role in the assessment and management of this complex oral disease.

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The most frequent sites involved in cGVHD at time of diagnosis are the skin, mouth, liver, and eyes (Lee & Flowers, 2008). Standard treatment of cGVHD consists of systemic immunosuppressive therapy, usually with steroids, for periods of two to seven years. That therapy, in addition to the chronic immunodeficiency and organ damage caused by the cGVHD, contributes to increased morbidity and mortality (Lee & Flowers, 2008). Although optimal treatment is not yet available for cGVHD manifesting in the oral cavity, patients with oral cGVHD need to receive the best available therapy to decrease disease severity and related symptoms, as well as to minimize the associated negative effects on their health-related quality of life (HRQOL) and nutritional status (Fall-Dickson et al., 2010).

Clinical Presentation

Oral involvement often is the first manifestation of the disease (Imanguli et al., 2006). Almost 80% of patients with cGVHD have oral clinical signs, including atrophy, edema, erythema, lichenoid changes, ulcers, and late fibrosis, which often lead to poor jaw range of motion (Imanguli et al., 2006). Lichenoid changes are similar in clinical presentation to oral lichen planus and have a
white lacy appearance in the oral cavity (Imanguli et al., 2008). Xerostomia, perceived oral dryness, viral and fungal infections, and side effects related to the immunosuppressant agents can further exacerbate oral pain and discomfort (Fall-Dickson et al., 2010). Early recognition and treatment of oral cGVHD is imperative to prevent increased pain and discomfort, as well as oral infections.

Diagnostic and Severity Scoring Criteria

Distinctive signs of oral cGVHD (e.g., xerostomia, mucositis, mucosal atrophy, pseudomembranes, ulceration) support the diagnosis, but the presence of these signs alone is insufficient to establish the diagnosis. The diagnosis must be supported by histologic evidence (Treister, Schubert, & Fall-Dickson, 2009). Clinical diagnosis of oral cGVHD requires at least one diagnostic manifestation (e.g., lichenoid changes, hyperkeratotic plaques, restriction of mouth opening) or at least one distinctive manifestation plus histologic confirmation by biopsy. Oral biopsy is necessary to differentiate between oral cGVHD and other oral conditions such as eczema, as well as infections, medication side effects, or hormonal imbalances (Lee & Flowers, 2008; Morton & Fontaine, 2011). In addition, manifestations such as gingivitis, mucositis, erythema, and oral pain are common to both acute and chronic oral GVHD (Filipovich et al., 2005).

The consensus document written by Filipovich et al. (2005) presents criteria for diagnosis and scoring (a global assessment of severity) of cGVHD in an attempt to standardize classification of the disease. Those criteria have been adopted for use in clinical trials designed to examine the efficacy of novel treatments for the disease. Those criteria may include organ- or site-specific outcomes such as oral cGVHD severity and related oral pain intensity, oral sensitivity, perceived oral dryness, HRQOL, and nutritional status. Oral cGVHD scoring criteria are presented in Figure 1.

Methods

A review of the literature was performed using PubMed records from 2006–2012. The key search terms used were cGVHD versus host disease, oral cGVHD, treatment of cGVHD, and clinical trials for treatment of oral cGVHD. In addition, references were selected from the reference lists of relevant articles found during the initial search. The National Institutes of Health (NIH) Clinical Trials.gov database also was searched. Thirteen articles describing research studies examining treatment for cGVHD were identified and included in this review (see Table 1).

Findings

Topical and Local Therapy

Of the nine research studies reviewed using topical or local therapies, four investigated budesonide. The remaining studies described novel therapies used to treat oral cGVHD. Budesonide, a topical synthetic glucocorticoid, is commonly used to treat oral cGVHD (Imanguli et al., 2006). Sari et al. (2006) performed a cohort analysis comparing outcomes of two treatment groups. Twelve patients received an oral budesonide rinse, in addition to the IV prednisone and cyclosporine they were receiving for treatment of cGVHD. Those 12 patients were compared to 11 patients receiving the IV prednisone and cyclosporine alone regarding improvement in oral cGVHD using the NIH consensus criteria. A single expert grader obtained oral assessments twice a week. Statistically significant differences were found from baseline and between groups in median oral examination scores and self-reported oral pain scores. Participants in the budesonide rinse group had decreased oral cGVHD scores and decreased self-reported pain scores.

In 2008, the pharmacokinetics and pharmacodynamic action of orally and buccally administered budesonide were investigated (Dilger et al., 2009). Bioavailability, as measured by systemic exposure of 12 participants using six different buccal budesonide doses, was compared to oral dosing. Interestingly, the oral cGVHD affected buccal CYP3A enzyme activity, which increased the drug’s uptake via impaired mucosa. The researchers concluded that buccal administration was as safe as oral administration, and similar pyruvate kinase (PK) levels were shown with both methods of administration.

Elad et al. (2012) examined improvements in oral cGVHD with an effervescent tablet preparation of budesonide. In this open, randomized, multicenter trial, objective responses of patients with oral cGVHD to various dosing protocols of this new budesonide preparation were examined. Patients were randomized into one of four treatment arms, each testing a different dose. Although the severity of oral cGVHD was reduced in all treatment arms, no statistically significant difference existed between the treatment arms.

Finally, a multicenter, phase III randomized trial examining the efficacy and tolerability of budesonide 3 mg effervescent tablets compared to placebo is underway (ClinicalTrials.gov, 2013b). One hundred and twenty six participants are planned to be enrolled in this study.

Five other studies were reviewed that tested various topical or local therapies. Mawardi, Stevenson, Gokani, Soiffer, and Treister (2010) reviewed records of patients treated with a combination of dexamethasone (a synthetic steroid) and tacrolimus (TAC) solutions, retrospectively. TAC (FK-506) is a macrolide immunosuppressant agent derived from the Streptomyces tsukubaensis

![FIGURE 1. National Institutes of Health Oral Chronic Graft- Versus-Host Disease Scoring Instrument Criteria](image-url)
TABLE 1. Research Testing Therapies for Oral Chronic Graft-Versus-Host Disease (cGVHD)

<table>
<thead>
<tr>
<th>Agent and Study</th>
<th>Design and Sample</th>
<th>Results</th>
<th>Oral Outcomes</th>
<th>Major Complications</th>
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<tr>
<td>Alemtuzumab subcutaneous (10 mg per day for three days)/rituximab IV (100 mg on day +4, +11, +18, and +25) (Gutiérrez-Aguirre et al., 2012)</td>
<td>Prospective analysis (N = 15)</td>
<td>100% response by day 30: 10 patients (67%) demonstrating partial remission, 5 (33%) demonstrating complete remission of GVHD</td>
<td>Almost 87% had oral manifestations of oral cGVHD with 100% response, either partial or chronic</td>
<td>Fever and chills, diarrhea, and leukemia relapse</td>
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<tr>
<td>Budesonide 3 mg tablet dissolved in 10 ml water with varying rinse duration times and times of day (Elad et al., 2012)</td>
<td>Open, randomized, multicenter phase II pilot with four arms (N = 16)</td>
<td>100% response, independent of treatment arm</td>
<td>Severity of oral cGVHD was reduced</td>
<td>Mild (six adverse events), and moderate (two adverse events): cheilitis, esophagitis, fungal infection, and taste alteration</td>
</tr>
<tr>
<td>Budesonide buccal versus oral 3 mg, 6 mg, or 9 mg in 10 ml aqueous solution mouthwash (Dilger et al., 2009)</td>
<td>Bioavailability comparison study using six treatment arms of different dosing regimens (N = 12)</td>
<td>Increased bioavailability with oral cGVHD present compared to healthy individuals</td>
<td>Presence of oral cGVHD increased uptake of the drug</td>
<td>Oral candidiasis</td>
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<tr>
<td>Budesonide rinse (3 mg coated capsule crushed and dissolved in 10 ml of water, used for 15 minutes three or four times daily) in addition to combined IV prednisone/IV cyclosporine versus combined IV prednisone/IV cyclosporine alone (Sani et al., 2006)</td>
<td>Cohort analysis with retrospective outcome assessments (N = 23; 12 drug, 11 placebo)</td>
<td>10 with overall response, 2 with stable disease and progression</td>
<td>Improvement in Oral Mucositis Rating Scale scores and oral pain as measured by visual analog scale</td>
<td>One patient had oral burning.</td>
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<tr>
<td>Combined dexamethasone (0.5 mg/5 ml)/tacrolimus (0.5 mg/5 ml) (Mawardi et al., 2010)</td>
<td>Retrospective record review (N = 14)</td>
<td>Improvement in oral cGVHD and related symptoms of pain, sensitivity, and dryness in the majority of participants</td>
<td>Decreased oral pain, oral dryness, and oral sensitivity; improved score rating for erythema and lichenoid changes with National Institutes of Health criteria</td>
<td>None</td>
</tr>
<tr>
<td>Mesenchymal stem cell expansion IV (Pérez-Simon et al., 2011)</td>
<td>Feasibility and safety phase II clinical trial (N = 18; 8 with cGVHD)</td>
<td>10 of 18 participants demonstrated overall response</td>
<td>Two responders</td>
<td>Three deaths attributed to disease, a liver biopsy, and toxicodermia. Deaths not attributable to the mesenchymal stem cell expansion.</td>
</tr>
<tr>
<td>Platelet lysate isoform AB mucoadhesive (Del Fante et al., 2011)</td>
<td>Pilot study for feasibility, safety, and efficacy of this delivery system (N = 7 total, 6 with cGVHD)</td>
<td>No response in patient with grade IV mucositis, but two patients with grade III mucositis had 100% response, one with grade III mucositis had 25% response, and three with grade III mucositis had 50% response.</td>
<td>Two with complete restoration of the integrity of the oral mucosa; four with at least 25% reduction in oral wound surface</td>
<td>None</td>
</tr>
<tr>
<td>Rituximab 375 mg/m² IV weekly (Zaja et al., 2007)</td>
<td>Retrospective analysis (N = 38)</td>
<td>65% of participants had active control of various oral cGVHD manifestations</td>
<td>48% overall response, 14% complete response, and 52% no response</td>
<td>No deaths were related to the rituximab therapy. Eight of 38 deaths were attributed to cGVHD progression, disease relapse, infections, and sudden death.</td>
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<tr>
<td>Rituximab weekly IV infusions of 375 mg/m² (Kim et al., 2010)</td>
<td>Prospective analysis (N = 37)</td>
<td>8 complete response and 24 partial response</td>
<td>28 participants had clinical signs of oral cGVHD 71% overall response; 4 had complete response, 16 had partial response, and 8 showed no response</td>
<td>Deaths from pneumonia, sepsis, pulmonary hemorrhage, infection after neutropenia, and a fall, not necessarily attributable to the therapy (Continued on the next page)</td>
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bacterium found in a soil fungus in Japan (Free Dictionary, n.d.). Fourteen patients who had been treated with the combination therapy were included. NIH total scores for oral cGVHD were examined at baseline, at follow-up 1 time period (12–49 days), and at follow-up 2 time period (49–86 days). The median improvement in oral erythema and lichenoid changes scores, self-reported oral pain, and self-reported oral sensitivity all were statistically significant at follow-up 2 in all participants.

St. John et al. (2013) evaluated the impact of topical thalidomide gel 20 mg in patients with oral ulcerative cGVHD in a phase II, randomized, placebo-controlled, double-blind clinical trial. Preliminary results suggested that topical thalidomide gel 20 mg has single-agent activity for oral cGVHD. The oral therapy also appears to be effective in relieving oropharyngeal pain related to oral ulcerative cGVHD. In addition, topical thalidomide decreased tumor necrosis factor alpha and interleukin 6 expression levels in oral saliva and oral ulcer exudates in patients with oral ulcerative cGVHD.

Del Fante et al. (2011) conducted a pilot study in Pavia, Italy, looking at the effect of platelet-derived growth factors on tissue healing in oral mucositis. Six of the seven patients had a positive response in healing as evidenced by cell growth. The one nonresponder was young (aged 13 years) and had ulcerative colitis in addition to allogeneic HSCT, which may have impaired the response.

The final clinical trial of topical or local therapies for oral cGVHD reviewed was an ongoing randomized, double-blind, placebo-controlled pilot examining the safety and efficacy of oral ulcerations' total surface area, as well as decreased oral pain intensity and cytokine expression in oral mucosa in thalidomide gel group. In the patients with oral ulcerative cGVHD, use of rituximab allowed the “reduction of baseline immunosuppressive therapy in 6 of 10 responding patients” (Zaja et al., 2007, p. 274), demonstrating clinical significance.

Kim et al. (2010) investigated weekly, followed by monthly, IV rituximab treatments for steroid-refractory cGVHD in patients in Seoul, South Korea. The prospective, multicenter, phase II trial used NIH criteria and evaluated patient quality of life, disease activity, and response to drug for one year. Biomarkers also were assessed. In the 28 patients with oral cGVHD, the overall response rate to the drug, as measured by the NIH criteria, was about 71%; the patient’s oral cGVHD lesions resolved and remained stable at the 14-month follow-up. This was the first reported case of successful resolution of steroid-recalcitrant cGVHD treated with topical TAC with custom trays.

### Systemic Therapy

Four clinical trials were reviewed that investigated a systemic treatment of cGVHD. Rituximab, an anti-CD20 chimeric monoclonal antibody, was investigated in two of those studies. The Gruppo Italiano Tapianto Midollo Osseo performed a retrospective review of rituximab in the treatment of refractory cGVHD in 38 patients (Zaja et al., 2007). Rituximab was given via IV at the conventional dose of 375 mg/m² weekly. Response rate and response duration were two of the outcomes investigated. Forty-eight percent of the patients with oral cGVHD had significant improvement in oral lesions or dryness (19% complete response, 29% partial response). Median time to response and median response duration were 46 days and 11 months, respectively. Notably, in the patients with oral cGVHD, use of rituximab allowed the “reduction of baseline immunosuppressive therapy in 6 of 10 responding patients” (Zaja et al., 2007, p. 274), demonstrating clinical significance.

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Altered health maintenance
- Encourage routine oral care.
- Dental visits as recommended

Altered nutrition: Less than body requirements
- Liquid or soft diet; advance as tolerated
- Encourage family to bring food from home.
- Small frequent meals
- Nutritional supplements such as Boost® or Ensure®
- Consult nutritionist.

Anticipatory grieving
- Pastoral care visit
- Support group
- Counseling

Anxiety or distress
- Provide a calming and relaxing environment.
- Encourage friends and family to spend time with patient.
- Meditation
- Alternative therapies (e.g., acupuncture, music therapy)

Decreased quality of life
- Encourage patient to function as independently as he or she is able.
- Encourage patient to continue with regular activities and roles as he or she is able.

Disturbed body image
- Encourage patient to identify positive self-thoughts.
- Allow patient to dress in own clothing rather than hospital clothing.

Infection
- Infection control measures via standard precautions
- Institute isolation precautions
- Daily skin care around oral mucosa
- Frequent oral care
- Advise patient to avoid sick contacts.

Impaired tissue integrity or altered oral mucous membrane
- Oral care several times per day
- Educate patient and family about oral care.
- Administer medications that help reduce cGVHD symptoms as ordered.

Pain
- Administer pain medications as ordered.
- Soft diet
- Alternative therapies (e.g., massage, acupuncture, music therapy)
- Meditation
- Avoid salty or acidic beverages.
- Palliative care consultation

FIGURE 2. Nursing Diagnosis and Interventions for Oral Chronic Graft-Versus-Host Disease (cGVHD)

4 patients had complete response, 16 had partial response, and 8 had no response. Oral cGVHD showed better responses than reported in prior studies. The authors concluded that systemic rituximab therapy in patients with cGVHD may reduce “clinical manifestations, permit steroid discontinuation, and improve quality of life in patients with the disease” (Kim et al., 2010, p. 1942).

Subcutaneous alemtuzumab and IV rituximab in combination was studied by Gutiérrez-Aguirre et al. (2012). Fifteen patients received one cycle of treatment drugs with a 100% response rate. Although the study did not specifically examine oral cGVHD, about 87% of participants had involvement of the oral mucosa, representing the highest percent of involvement in the study. Reported adverse effects included infection (Gutiérrez-Aguirre et al., 2012).

The final study examined expanded mesenchymal stem cells (MSC) in the treatment of cGVHD. Pérez-Simon et al. (2011) studied patients in the Hospital Clinico Universitario de Salamanca in Spain. Although the study did not specifically look at treatment of oral cGVHD, three patients with oral cGVHD were enrolled. Most prior studies of MSCs have been targeted at acute GVHD. This feasibility and safety study looked at both acute and cGVHD. Although one patient with oral cGVHD was reported as deceased from complications of cGVHD at last follow-up, the other two patients with oral cGVHD had a response to treatment with a duration of at least one year. The authors found no adverse events that were directly related to MSC infusion (Pérez-Simon et al., 2011).

Implications for Nursing

Oral involvement of cGVHD is seen in the majority of patients with the disease (Lee & Flowers, 2008). Although the therapies described here have demonstrated promising results and warrant additional research, no optimal treatment exists for oral cGVHD at this time. Normal eating habits and nutritional intake are significantly impacted by oral ulcerations (Elad et al., 2012). Patients with the oral disease suffer pain and discomfort, as well as an impaired HRQL (Fall-Dickson et al., 2010). Nurses working with post-HSCT recipients at the bedside and in advanced practice nursing roles, including nurse practitioners and clinical nurse specialists, will encounter patients with oral cGVHD. Those patients must be assessed routinely for oral cGVHD-related signs and symptoms, as well as salivary involvement-related manifestations of perceived oral dryness and xerostomia. Monitoring for secondary infections, such as herpes simplex, candida, and cytomegalovirus, must be included in the nurse assessment. Nursing diagnoses and nursing actions appropriate for this patient population are presented in Figure 2. Nurses play a key role in assessment and management of this complex oral condition, as well as direct involvement in clinical research testing novel topical and systemic interventions for this complex oral disease.

References


