Oral chronic graft-versus-host disease in Australia: clinical features and challenges in management

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Key words
graft-versus-host disease, oral mucosa, saliva.

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Abstract
Data from the Australasian Bone Marrow Transplant Recipient Registry show a steady increase in the number of allogeneic haemopoietic stem cell transplantations (HSCT) performed annually in Australia and New Zealand. In 2012, 629 allogeneic HSCT were performed. Allogeneic HSCT is associated with numerous potential complications, including chronic graft-versus-host disease (cGVHD). The oral cavity is one of the most frequent sites affected by cGVHD, often leading to significant disability and reduced quality of life. Management strategies are often complex, of variable efficacy and influenced by the availability of various therapeutic agents, access to compounding pharmacies and associated costs. This paper summarises the current status of allogeneic HSCT in Australia and New Zealand with a focus on oral cGVHD and the associated challenges in its management.

Introduction
Allogeneic haemopoietic stem cell transplantation (HSCT), along with the accompanying immunosuppression, is associated with several, potentially debilitating, long-term complications, one of the most significant being chronic graft-versus-host disease (cGVHD). cGVHD is a multisystem immune disorder characterised by immune dysregulation, immunodeficiency, impaired organ function and decreased survival.1 Nearly 50% of patients who survive longer than 1 year after HSCT develop cGVHD.2 Factors influencing the risk of cGVHD onset overall include the use of mobilised peripheral blood stem cells as opposed to bone marrow as the graft source, older donor and patient age and the use of unrelated donors.3 All of these factors are increasingly common in HSCT practices internationally and will likely result in increased presentations of oral cGVHD. Specific risk factors for the development of oral cGVHD are less well established with the use of peripheral blood stem cells and a prior history of cGVHD identified in the literature.4

Management of cGVHD remains a significant challenge. One of the most frequent sites affected by cGVHD is the oral cavity which may be the primary or sole site of involvement.5 Oral cGVHD has a significant and detrimental impact on oral health, function and quality of life.

Therapeutic decisions in the management of oral cGVHD must consider the patient’s global disease status and must require close liaison with the patient’s transplant physician. Critically, data are scarce on the efficacy of the commonly utilised topical and systemic agents in the management of oral cGVHD with the effectiveness of these agents presumed by extrapolating from their effectiveness in the management of more common, immune-mediated mucosal diseases, such as oral lichen planus (OLP). Management strategies vary between transplant centres and are often based on institutional practices and influenced by the availability of particular agents and formulations, patient acceptance and cost.6

Allogeneic HSCT in Australia
Allogeneic HSCT has evolved as a curative therapy for haematological malignancy, bone marrow failure, immune deficiencies and some solid tumours. The Australasian Bone Marrow Transplant Recipient Registry has

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a comprehensive database of transplant activity since 1992. Registry figures demonstrate a steady annual growth in the number of allogeneic HSCT performed in Australia and New Zealand. A total of 570 allogeneic transplants was undertaken in 2013, representing an increase of 16% over a 5-year period. The most common indication for allogeneic transplantation in Australia and New Zealand, as it is internationally, is acute myeloid leukaemia in both the related donor (34%) and unrelated donor (35%) transplant setting.

GvHD is a common transplant-associated complication following allogeneic HSCT, second only to infection and is, directly or indirectly, the major cause of early mortality following allogeneic HSCT. GvHD is an alloimmune complication of HSCT occurring as a consequence of tissue injury resulting from proliferation of donor T cells and release of inflammatory cytokines. It is traditionally distinguished into acute (<100 days post-HSCT) and chronic GvHD, although this distinction has been blurred by changes in transplant practices, most notably the increased use of reduced-intensity conditioning transplant regimens. Acute GvHD classically affects the skin, gastrointestinal tract and liver. In contrast, cGvHD is an immunoregulatory disorder with features of both autoimmunity and immunodeficiency and may affect any organ. cGvHD is the main cause of late non-relapse mortality and morbidity following HSCT and is the major determinant of quality of life in HSCT survivors.

The clinical spectrum and diagnosis of oral cGvHD

The reported incidence of oral cGvHD varies widely with 45–83% of patients who experience cGvHD showing features of oral involvement. Presentations include characteristic lichenoid mucosal lesions, xerostomia secondary to salivary gland involvement or a reduction in oral aperture, resulting from local sclerodermatous disease of the skin.

Mucosal chronic GvHD

In 2005–2006, the National Institutes of Health proposed simplified and standardised criteria for the diagnosis and staging of cGvHD. The range of clinical signs and symptoms seen in cGvHD was divided by site or organ involved and each feature assigned to either: (i) those deemed to be diagnostic for cGvHD (termed diagnostic features) and (ii) those insufficient, when arising alone, to secure a diagnosis of cGvHD due to their non-specific nature (termed distinctive features).

Specific to the oral cavity, the signs and symptoms identified by the National Institutes of Health consensus papers as diagnostic or distinctive for the presence of oral cGvHD are listed in Table 1. These oral mucosal diagnostic features closely resemble with, clinically and histologically, common autoimmune disorders, including scleroderma and OLP. Any oral site may be affected; however, the buccal mucosa, tongue and labial mucosa are most commonly affected. The degree of involvement may be extensive (Figs 1,2) and lesions can be a source of significant pain, limiting nutritional intake and impeding overall quality of life.

Other conditions, common in the transplant patient may bear a resemblance to the clinical features of oral cGvHD and may potentially lead to a misdiagnosis of cGvHD. Infections, including herpetic and fungal and mucosal trauma, are common in the immuno-

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Table 1 Classification of the signs and symptoms of chronic graft-versus-host disease (cGvHD)

<table>
<thead>
<tr>
<th>Features</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lichen-type features</td>
<td>Fixed, white striations (not removable with cotton gauze)</td>
</tr>
<tr>
<td>Hyperkeratotic plaques</td>
<td>Fixed, white plaques (not removable with cotton gauze)</td>
</tr>
<tr>
<td>Restriction of mouth opening from sclerosis</td>
<td>Fibrosis/hardening of the perioral tissues on palpation and reduction of oral aperture</td>
</tr>
<tr>
<td>Xerostomia†</td>
<td>The subjective complaint of oral dryness</td>
</tr>
<tr>
<td>Mucoceles</td>
<td>A usually painless, smooth surfaced mass. May appear clear or bluish in colour and be numerous (Fig. 2)</td>
</tr>
<tr>
<td>Mucosal atrophy†</td>
<td></td>
</tr>
<tr>
<td>Pseudomembranes†</td>
<td></td>
</tr>
<tr>
<td>Ulceration†</td>
<td></td>
</tr>
<tr>
<td>Gingivitis</td>
<td></td>
</tr>
<tr>
<td>Mucositis</td>
<td></td>
</tr>
<tr>
<td>Erythema</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td></td>
</tr>
</tbody>
</table>

†In all cases, infection, drug effects, malignancy or other causes must be excluded.

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compromised patient, especially those suffering from a dry mouth, and may resemble the white plaques and mucosal ulceration of oral cGvHD (Fig. 3). Simple clinical steps are often sufficient to exclude these confounding diagnoses and confirm a diagnosis of oral cGvHD. This may include smoothing of sharp teeth in the vicinity of mucosal trauma and using cotton gauze to identify if a white patch can be removed, as would be seen in candidosis. However, occasionally, particularly in the case of persistent oral ulceration, biopsy may be necessary both to confirm the presence of oral cGvHD and exclude malignancy. The histopathological features of oral cGvHD have been previously well described.\textsuperscript{13}

Salivary hypofunction and xerostomia

Salivary gland dysfunction arising in the acute stages following allogeneic HSCT is predominantly attributable to conditioning regimen toxicity, especially in the case of total body irradiation, and can persist for many months. Late changes are most often ascribed to cGvHD and clinically resemble the features of Sjögren syndrome.\textsuperscript{14}

Extensive involvement results in the total destruction of secretory units leading to permanent and profound salivary hypofunction.\textsuperscript{13} Salivary gland dysfunction can be the sole manifestation of oral cGvHD and most often presents as the complaint of dry mouth (xerostomia). Critically, the presence of salivary hypofunction is not diagnostic for oral cGvHD\textsuperscript{13} due to the existence of several other potential aetiologies, most notably drugs and/or radiotherapy to the head and neck.

Saliva plays a major role in maintaining oral health and oral function. A decrease in the quantity or quality of saliva can have a profound effect on the incidence of dental decay, oral candidosis, the retention of dentures and mucosal friability as well as an adverse impact on speech, swallowing and mastication. Critically, patients report oral dryness as the second most distressing symptom both at discharge and at 1 year after allogeneic HSCT.\textsuperscript{15} However, the symptom of xerostomia does not always correlate with clinical signs of salivary hypofunction; likewise, clinical evidence of a reduced
salivary flow may be demonstrable in patients who do not complain of a dry mouth.17

**Clinical management of oral chronic GvHD**

Topical preparations may be the sole therapy for oral cGvHD or may form part of a more complex management schedule. The advantages of topical or local therapies include the application of intensive treatments without necessarily increasing systemic immunosuppression thus maintaining any desirable graft-versus-tumour effects and avoiding systemic toxicities and drug interactions.6 Critical features of an effective topical or local therapy include substantivity (persistence of therapeutic effect), bioavailability when applied to oral mucosa, acceptable taste and a non-inhibitory cost.

The management of oral cGvHD can be divided into: (i) management of oral mucosal changes and (ii) management of the associated salivary hypofunction. A clinical algorithm for the management of symptomatic oral cGvHD is presented in Figure 4.

**Management of the oral mucosal lesions of cGvHD**

**Topical corticosteroids** The mainstay of topical therapy in the management of symptomatic oral cGvHD is steroid preparations formulated in a variety of vehicles, including gels, ointments and rinses, and with varying potency.18 The most commonly used formulations available in Australia are outlined in Table 2.

Transient burning and the development of secondary oral candidosis are the most common adverse effects of topical corticosteroid therapy. The generalised immunosuppressive and anti-inflammatory effects of topical corticosteroids are believed to play the major role in the pathogenesis of secondary oral candidosis.19 It has been reported that the presence of oral candidosis may lead to an increase in local symptoms,20 however, this is not universally accepted. The development of oral candidosis may delay effective management and obscure the original pathology of interest.21 Resolution is usually achievable with topical antifungal agents,20 which are generally prescribed in a prophylactic capacity throughout the course of topical steroid therapy. Several topical antifungal agents are available for use; selection of the appropriate vehicle requires consideration of the oral disease status, for example, patients with severely dry or ulcerated tissues do not tolerate the use of a lozenge (e.g. amphotericin B lozenge, Fungilin, Aspen Pharmacare Australia Pty Ltd, Sydney, NSW, Australia). An antifungal gel is usually utilised with miconazole gel (Daktarin Oral Gel, Johnson & Johnson Pacific Pty Limited, Sydney, NSW, Australia), the agent of choice; however, established drug interactions, especially with warfarin, must be considered (Table 2).

Data demonstrating systemic absorption following application of topical corticosteroids to the oral mucosa are lacking; however, caution is required in patients with widespread ulceration due to reduced mucosal barrier function and with prolonged or excessive use.22,23 Unlike the skin, oral mucosal atrophy is rarely a significant problem with long-term topical corticosteroid use; however, for patients with pre-existing mucosal atrophy, this may be compounded. For this reason, the use of the least potent agent to achieve therapeutic benefit and discontinuation of treatment when symptoms resolve is recommended.

**Alternative topical agents** Effective symptom management with topical corticosteroid therapy is not always achievable prompting the use of topical immunomodulators. A small number of studies has explored the use of topical cyclosporin where oral cGvHD was not responsive to topical corticosteroids. Promising results were shown with cyclosporin in both a mouth rinse and adhesive paste; however, sample size was insufficient to provide a high level of evidence.24,25 Side effects were reported as mild and usually consist of transient burning. While the topical cyclosporine mouthwash (Neoral solution, Novartis Pharmaceuticals Australia Pty Ltd, Sydney, NSW, Australia) has been utilised in some Australian transplant centres, it is prohibitively expensive and so is not routinely used. In addition, its unpleasant taste and high (12%) ethanol content makes this solution generally not suitable for the frequently ulcerated and atrophic presentations of oral cGvHD.

Tacrolimus and pimecrolimus are newer calcineurin inhibitors with an improved safety profile in comparison to cyclosporin. Tacrolimus is widely used in its topical preparation for the treatment of atopic dermatitis and cutaneous cGvHD. There have been promising results about the use of tacrolimus in the management of symptomatic OLP and the oral mucosal lesions of vesiculobullous conditions and Crohn disease, the majority of the studies concluded that tacrolimus was at least as effective as topical corticosteroids. This has been recently reviewed elsewhere.26

Importantly, tacrolimus ointment has shown success in a limited number of studies in patients with oral cGvHD.27,28 In clinical practice, there is often a preference for the use of topical tacrolimus where oral cGvHD involves the lips and vermilion as a means for avoiding the potential atrophic effects seen with prolonged topical corticosteroid use in these sites. The use of topical tacrolimus in the management of oral mucosal disease has
Figure 4 Clinical algorithm for symptomatic management of mucosal oral chronic graft-versus-host disease (cGvHD).

The appropriate topical antifungal agent should be selected for each patient with reference to GvHD presentation and potential drug interactions.

* Follow-up patient should be reviewed at 4 weeks to confirm maintenance of symptom control. Blennorhagic mucositis surveillance recommended.
been shown to have reasonable safety and few adverse effects with those documented, including the sensation of mucosal burning, taste disturbance and mucosal staining.26 Systemic absorption, with therapeutic trough levels, has been reported by some;29 however, it is unclear if whole blood tacrolimus levels need to be continuously assessed in patients receiving topical tacrolimus alone, although patients receiving concurrent systemic tacrolimus should be closely monitored.

While tacrolimus ointment generally has an acceptable toxicity profile, the United States Food and Drug Administration issued a ‘black box’ warning for tacrolimus due to a theoretical increased risk of malignancy, specifically squamous cell carcinoma (SCC) and lymphoma, when used for cutaneous psoriasis.30 In Australia, the use of topical tacrolimus is also inhibited by the need for a compounding pharmacist. Ideally, tacrolimus is compounded with orabase to form a 0.1% ointment. Paraffin wax has been used for skin preparations; however, this is not suitable for oral use due to poor adhesion. For these reasons, tacrolimus use is limited and often restricted to second-line therapy when treatment with topical corticosteroids has failed.

Non-pharmacological management strategies form a critical adjunct in the overall management of patients suffering from oral mucosal cGvHD. This includes the avoidance of known irritants, such as sodium lauryl sulphate (SLS)-containing toothpastes and alcohol-containing mouthwashes. Suitable products are readily available; some commonly used products are highlighted in Table 3. A bland diet is recommended and often better tolerated with the avoidance of spices, chilli and acidic foods during symptomatic phases. The use of topical analgesics, such as lignocaine viscous (2% solution, 15 mL swished for 30 s every 3 h) may be helpful when symptomatic oral cGvHD impedes daily activities and nutritional intake.

Table 2 Topical corticosteroids plus common anti-fungal medications used in the management of oral chronic graft-versus-host disease

<table>
<thead>
<tr>
<th>Potency</th>
<th>Generic name</th>
<th>Concentration</th>
<th>Brand</th>
<th>Instructions for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (Class I)</td>
<td>Hydrocortisone acetate</td>
<td>1.0% ointment</td>
<td>Sigmatic</td>
<td>Apply thin film 2–4 times daily after meals</td>
</tr>
<tr>
<td>Moderate (Class II)</td>
<td>Triamcinolone acetonide</td>
<td>0.02% ointment, 0.1% emollient</td>
<td>Aristocort, Kenalog in orabase</td>
<td>Apply thin film 2–3 times daily after meals</td>
</tr>
<tr>
<td></td>
<td>Betamethasone valerate</td>
<td>0.02%, 0.05% ointment</td>
<td>Betnovate</td>
<td>Apply thin layer 2–3 times daily after meals</td>
</tr>
<tr>
<td></td>
<td>Fluticasone propionate</td>
<td>125 mcg/dose inhaler</td>
<td>Flixotide metered dose</td>
<td>1–2 sprays directed at lesion, 2–4 times daily (max 8 spray doses per day)</td>
</tr>
<tr>
<td>Potent (Class III)</td>
<td>Betamethasone valerate</td>
<td>0.1% ointment</td>
<td>Betnovate</td>
<td>Apply thin film 2–3 times daily after meals</td>
</tr>
<tr>
<td></td>
<td>Betamethasone dipropionate</td>
<td>0.05% ointment</td>
<td>Diprosone</td>
<td>Apply thin film 2–3 times daily after meals</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone 4 mg tablet</td>
<td>0.25 mg/mL solution (0.5 mg/rinse)</td>
<td>One tablet dissolved in 160 mL water</td>
<td>Gently swish with 20 mL for 5 min then spit out. Repeat 3–4 times daily</td>
</tr>
<tr>
<td></td>
<td>Prednisolone 5 mg tablet</td>
<td>0.5% solution</td>
<td>Dissolve 1 tablet in 10 mL water</td>
<td>Gently swish with entire solution for 5 min then spit out. Repeat 3–4 times daily. Bitter taste may affect compliance- dexamethasone solution preferred.</td>
</tr>
<tr>
<td>Super potent (Class IV)</td>
<td>Mometasone furoate</td>
<td>0.1% ointment</td>
<td>Elocon</td>
<td>Apply thin film 1–2 times daily</td>
</tr>
<tr>
<td>Intra-lesional injection</td>
<td>Betamethasone dipropionate</td>
<td>0.05% OV</td>
<td>Diprosone OV</td>
<td>Apply thin film 1–2 times daily</td>
</tr>
<tr>
<td>Commonly used topical antifungals</td>
<td>Triamcinolone acetonide</td>
<td>10 mg/mL</td>
<td>Kenocort-A 10</td>
<td>Maximum 1 mg/injection site, repeat at ≥1 week intervals if required</td>
</tr>
<tr>
<td></td>
<td>Miconazole</td>
<td>20 mg/g</td>
<td>Daftarin Oral Gel</td>
<td>Place one-half of provided scoop on tongue, hold for as long as possible then swallow. Alternatively, patients using an ointment TC can mix both 1:1. Be aware of drug interactions, especially warfarin. Swirl 1 mL in mouth for as long as possible then swallow. Repeat four times a day. Alternatively, patients using mouthwash TC can add 1 drop to each mouth rinse. Contains sucrose – not for prolonged use in dentate patients</td>
</tr>
<tr>
<td></td>
<td>Nystatin</td>
<td>100,000 U/mL (dropper bottle)</td>
<td>Nilstat Oral Drops</td>
<td>Place one-half of provided scoop on tongue, hold for as long as possible then swallow. Alternatively, patients using an ointment TC can mix both 1:1. Be aware of drug interactions, especially warfarin. Swirl 1 mL in mouth for as long as possible then swallow. Repeat four times a day. Alternatively, patients using mouthwash TC can add 1 drop to each mouth rinse. Contains sucrose – not for prolonged use in dentate patients</td>
</tr>
</tbody>
</table>

OV, optimised vehicle; TC, topical corticosteroids.
Management of xerostomia

Successful management of the symptom of xerostomia associated with cGvHD is often enormously challenging. Temporary relief may be achieved through the use of oral moisturisers, chewing sugar-free gum, saliva substitutes and frequent sips of water. Artificial saliva products are available in various preparations with unique qualities, yet few studies have compared their effectiveness. One study compared the efficacy of commercially available mucin-based products with carboxymethylcellulose (CMC) preparations – finding that mucin-containing products were better tolerated and accepted by patients.31 Most available products, including those in Australia, are, however, CMC preparations, which increase the viscosity but do not reproduce the physical or chemical properties of saliva.32 Patient acceptance of these preparations is also often hindered by taste, viscosity, lubrication properties and poor retention in the mouth.33

Longer-lasting results may be seen with the use of sialagogues, such as pilocarpine hydrochloride, which directly stimulate the salivary glands to increase output. However, functional glandular tissue is required for successful outcomes of therapy. Pilocarpine is most commonly prescribed for the treatment of glaucoma as a locally acting meiotic agent of the papillary muscles. Through its cholinergic effect, pilocarpine hydrochloride also increases the secretions of exocrine glands, including the salivary, lacrimal, sweat and gastric glands, along with the mucous cells of the respiratory tract. In Australia, off-label uses of pilocarpine (Isopto Carpine eye drops, Alcon Laboratories Australia Pty Ltd, Sydney, NSW, Australia) occurs in numerous conditions associated with salivary hypofunction, namely, Sjögren syndrome and more recently salivary hypofunction in cGvHD (Table 3). Adverse effects seen with pilocarpine hydrochloride may include urinary urgency and an increase in perspiration, lacrimation and nausea. More

Table 3 Management of xerostomia in chronic graft-versus-host disease

<table>
<thead>
<tr>
<th>Use</th>
<th>Specific agent</th>
<th>Main ingredients</th>
<th>Instructions for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium lauryl sulfate-free toothpastes (fluoride containing)</td>
<td>Biotène toothpaste</td>
<td>0.14% w/v sodium monofluorophosphate</td>
<td>With all toothpastes: Patients should be instructed to brush their teeth at least twice daily using a soft brush.</td>
</tr>
<tr>
<td>Oral Seven toothpaste</td>
<td>0.76% w/v sodium monofluorophosphate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curasept chlorhexidine toothpaste</td>
<td>0.05% fluoride</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curaprox Enzymcal Xerostom toothpaste</td>
<td>0.05% chlorhexidine, Sodium fluoride 950 ppm, Sodium fluoride 995 ppm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sialagogues</td>
<td>4% Isopto Carpine eye drops (15 mL)</td>
<td>Pilocarpine hydrochloride</td>
<td>Online only</td>
</tr>
<tr>
<td>Mucosal lubricants</td>
<td>Biotène oral balance gel</td>
<td>Glycerin and sorbitol base, 1. Carboxomer, 2. Hydroxyethylcellulose, 3. Sodium hydroxide</td>
<td>Apply on fingertip to affected areas when required, especially at night. Biotène range: mouthwash, spray</td>
</tr>
<tr>
<td>Oral Seven gel</td>
<td>Glycerin, sorbitol base, 1. Aloe barbadensis, 2. Lactoperoxidase, 3. Glucose, 4. Lactoferrin, Lysozyme</td>
<td>Apply by fingertip to affected areas when required, especially at night. Oral Seven range: mouthwash, spray</td>
<td></td>
</tr>
<tr>
<td>Hamilton Aque Oral Gel</td>
<td>Carmellose sodium 20 mg/g</td>
<td>PBS approval for 4 months in palliative care where dry mouth is a symptom</td>
<td></td>
</tr>
<tr>
<td>Hamilton Aque Liquid</td>
<td>Per mL contains: Sorbitol solution 42.86 mg, Carmellose sodium10 mg</td>
<td>1–2 sprays into mouth as required. PBS approval for 4 months in palliative care</td>
<td></td>
</tr>
<tr>
<td>Xerostom Gel (Biocosmetic Laboratories)</td>
<td>Glycerin based, Extra virgin olive oil, Provitamin B3, Provitamin E, Parsley oil (See fact sheet for full list)</td>
<td>Apply by fingertip to affected areas when required, especially at night. Xerostom range: spray, pastilles, gum, mouthwash</td>
<td></td>
</tr>
<tr>
<td>General salad oils</td>
<td>Patients can use any palatable salad oil as an oral lubricant e.g. coconut oil, olive oil, etc.</td>
<td>Place a small amount in mouth, use tongue to spread over affected tissues</td>
<td></td>
</tr>
</tbody>
</table>

PBS, Pharmaceutical Benefits Scheme.
significant adverse effects include an increase in airway resistance and bronchial secretions as well as bradycardia and postural hypotension. Pilocarpine should therefore be avoided in patients with significant comorbidities, including pulmonary or gastrointestinal GvHD.

Several studies have shown promising results with pilocarpine therapy for patients who have had head and neck radiotherapy and, more recently, in patients with salivary cGvHD. One study demonstrated a statistically significant difference in salivary flow rate 1 h following administration of pilocarpine hydrochloride (5 mg oral pilocarpine, Salagen, Bausch & Lomb Incorporated, Tampa, FL, USA). This same research also found that saliva levels rapidly returned to baseline following cessation of treatment, suggesting that continuous administration is necessary. While longer-acting sialagogues have been studied in cGvHD (cevimeline – Evoxac, Daiichi Sankyo, Parsippany, NJ, USA), none of these is currently available in Australia. Common products used for the management of dry mouth are listed in Table 3.

Patients should also be encouraged to use a fluoride-containing toothpaste that is free of SLS, as this is often better tolerated. Detailed oral hygiene and dietary instruction are also essential. Saliva is a reservoir for ions that facilitate tooth remineralisation and so avoidance of acidic and sugar-containing foods and beverages are essential in minimising the rampant dental decay that is frequently seen in patients with low salivary flow.

**Prognosis and long-term screening**

Survivors of allogeneic transplantation face a significant risk of secondary malignancies, with 2–6% of survivors developing a secondary solid malignancy at 10 years. SCC of the skin and mouth account for one-third of all developing a secondary solid malignancy at 10 years. Risk factors specific for secondary solid tumours in this group with half of these specifically Fanconi anaemia), a history of cGvHD and total body irradiation in the conditioning regimen. The degree of immunosuppression has also been investigated as a risk factor for secondary solid tumours. While both systemic and topical immunosuppressive therapy have been suggested as potential risk factors, for oral SCC, exposure to these therapies and the presence of cGvHD are so closely interconnected that it is not possible to attribute specific carcinogenic risk.

Examination and surveillance of the oral tissues of survivors of allogeneic HSCT, with timely biopsy of persistent or suspicious lesions to exclude dysplasia or malignancy, should form part of the long-term follow up and screening following transplantation. Ideally, this should be conducted by experienced Oral Medicine specialists in close collaboration with the bone marrow transplant (BMT) team. Guidelines on the long-term management of patients with Fanconi anaemia recommend oral mucosal review on a 6-monthly basis while recently published consensus guidelines on the long-term follow up of transplant recipients recommend annual oral mucosal review.

**Conclusion**

Allogeneic transplantation is increasingly used for a range of diseases in children and in adults. With improvements in transplantation science, human leucocyte antigen-typing and supportive care, more patients can anticipate long-term survival following HSCT. Unfortunately, many survivors experience cGvHD with oral GvHD, a major cause of morbidity and a significant determinant of post-HSCT quality of life. Appropriate management of oral cGvHD is compromised by a paucity of good quality evidence, but there are guidelines to optimise oral outcome after BMT and these should be referenced in all BMT service protocols.

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**References**


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