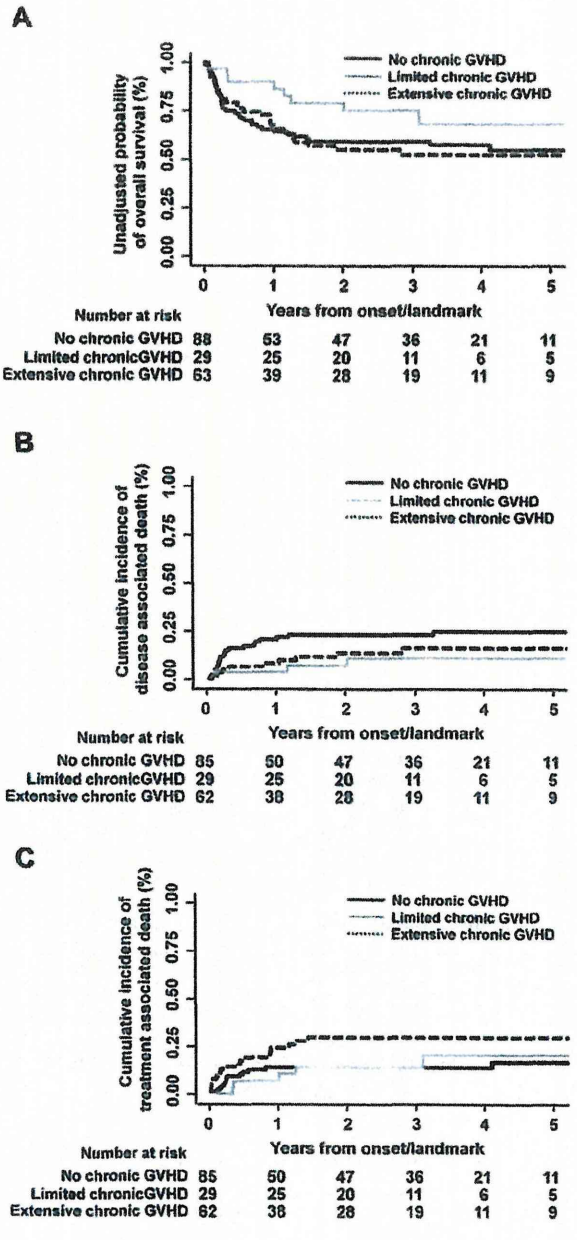

Figure 3. Semi-landmark plots for impact of chronic GVHD. Semi-landmark plots illustrating impact of chronic GVHD on overall survival (A), disease-associated mortality (B), and treatment-related mortality (C).

suggested the trend toward a reduced risk of disease-associated deaths in the limited chronic GVHD group.

Our present findings are in contrast to the previous reports showing the beneficial effects of chronic GVHD rather than acute GVHD on the prevention of disease recurrence after allogeneic HCT. It is less likely that the particular characteristics of chronic GVHD in patients with ATL biased the results, because the incidence rate and median onset day of chronic GVHD in our cohort were similar to those reported in previous studies evaluating the incidence of chronic GVHD among Japanese patients, most of whom had received allogeneic HCT for myeloid neoplasms or acute lymphoblastic leukemia.[30-32] Conceivably, the rapid tempo of disease recurrence of ATL might be such that chronic GVHD is less potent in terms of harnessing clinically relevant graft-versus-leukemia responses compared with acute GVHD. However, the results of our analysis regarding the effect of chronic GVHD should be interpreted with caution because the number of patients evaluable for chronic GVHD was relatively small in our study for providing sufficient statistical power. The effect of chronic GVHD on outcomes after HCT for ATL should be further explored in a larger cohort.

The occurrence of GVHD has been shown to exert a potent graft-versus-leukemia effect in terms of reducing relapse incidence in acute leukemia or chronic myeloid leukemia.[33,34] In contrast, multiple studies have documented a correlation between GVHD in its acute or chronic form and treatment-related mortality. In a study of patients undergoing HLA-identical sibling HCT for chronic myeloid leukemia, the overall beneficial effect on long-term survival was demonstrated only in a group of patients who developed grade 1 acute GVHD or limited chronic GVHD.[33] In another study of HLA-identical sibling HCT for leukemia using cyclosporine and methotrexate as GVHD prophylaxis, a benefit of mild GVHD was only seen in high-risk patients but not in standard-risk patients. Therefore, the therapeutic window between decreased relapse incidence and increased transplant-related mortality in association with the development of GVHD has been considered to be very narrow.[34]

With regard to the effectiveness of allogeneic HCT for ATL, it is also of note here that posttransplant eradication of ATL cells can be achieved without the use of high-dose chemoradiotherapy: patients who received a transplant with reduced intensity conditioning had survival outcomes similar to those who received a transplant with myeloablative conditioning in our study. Intriguingly, several small cohort studies exhibited that abrupt discontinuation of immunosuppressive agents resulted in disappearance or reduction in the tumor burden in allografted patients with ATL. In some cases, remission of ATL was observed along with the development of GVHD.[19,20,22] Taken together with the findings of this study, it is suggested that ATL is particularly susceptible to immune modulation following allogeneic HCT. To clarify the presence of such "graft-versus-ATL" effect, further investigations are needed to assess the efficacy of donor lymphocyte infusion or withdrawal of immunosuppressive agents on relapse after transplantation.

Of the HTLV-I gene products, Tax is a dominant target of HTLV-I–specific cytotoxic T lymphocytes. The vigorous Tax-specific cytotoxic T-cell responses were demonstrated in recipients who obtained complete remission after allogeneic HCT for ATL, suggesting that "graft-versus-HTLV-I" responses might contribute to the eradication of ATL cells.[35,36] However, Tax is generally undetectable or present in very low levels in primary ATL cells.[37,38] In addition, small amounts of HTLV-I provirus can be detected in peripheral blood of recipients who attained long-term remission of ATL, even after HCT from HTLV-I–negative donors.[39,40] These findings suggest that "graft-versus-ATL" effect can be harnessed without complete elimination of HTLV-I. It is also important to note that allogeneic HCT is emerging as an effective treatment option for other mature T-cell neoplasms not related to HTLV-I, such as mycosis fungoides/Sézary syndrome and various types of aggressive peripheral T-cell lymphomas.[41,42] These observations raised the possibility that the common targets for alloimmune responses might exist across a spectrum of malignant T-cell neoplasms, including ATL. The minor histocompatibility antigens or tumor-specific antigens can be other targets of alloimmune anti-ATL effect.[43-45] Therefore, the elucidation of the mechanism underlying an immunologic eradication of primary ATL cells may

Table 3. Effect of chronic GVHD on overall survival, disease-associated mortality, and treatment-related mortality after allogeneic hematopoietic cell transplantation for adult T-cell leukemia

Outcome	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Overall survival*				
Limited chronic GVHD vs no chronic GVHD	0.71 (0.34-1.47)	.353	0.72 (0.35-1.50)	.385
Extensive chronic GVHD vs no chronic GVHD	1.45 (0.90-2.35)	.131	1.40 (0.86-2.30)	.176
Disease-associated mortality†				
Limited chronic GVHD vs no chronic GVHD	0.45 (0.14-1.46)	.183	0.45 (0.14-1.44)	.178
Extensive chronic GVHD vs no chronic GVHD	0.81 (0.39-1.67)	.563	0.80 (0.39-1.64)	.536
Treatment-related mortality‡				
Limited chronic GVHD vs no chronic GVHD	1.59 (0.64-3.95)	.316	1.56 (0.63-3.87)	.342
Extensive chronic GVHD vs no chronic GVHD	2.85 (1.41-5.77)	.004	2.75 (1.34-5.63)	.006

*There was no significant variable.
†There was no significant variable.
‡There was no other significant variable.

lead to a new strategy for improving outcomes of allogeneic HCT not only for ATL but also for other intractable T-cell neoplasms.

This study has several limitations. First, acute GVHD might be intentionally induced for some patients considered at high risk of relapse by treating clinicians. Second, the information on the day when each grade of GVHD occurred was not available. Therefore, we treated the development of acute and chronic GVHD in their worst severity as a time-varying covariate. To validate the results, we also performed the landmark analysis and obtained consistent results. Third, the relatively small number of patients with chronic GVHD might mask or bias the effect of chronic GVHD on outcomes. Last, the effect of multiple testing should be taken into account for the interpretation of the secondary end points.

In conclusion, the development of acute GVHD was associated with lower disease-associated mortality after allogeneic HCT for ATL compared with the absence of acute GVHD. However, improved survival can be expected only among a group of patients who developed mild-to-moderate acute GVHD because those who developed severe acute GVHD were at high risk of treatment-related mortality. New strategies that enhance the allogeneic anti-ATL effect without exacerbating GVHD are required to improve the outcomes of patients undergoing allogeneic HCT for ATL.

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Authorship

Contribution: T.I. and T.U. designed the research and organized the project; M. Hishizawa, J.K., T.I., and T.U. reviewed and analyzed data and wrote the paper; J.K., T.I., and K.M. performed statistical analysis; Y.A., R.S., and H.S. collected data from JSHCT; T.K. and Y. Morishima collected data from JMDP; T.N.-I., and S. Kato collected data from JCBBN; and A.U., S.T., T.E., Y. Moriuchi, R.T., F.K., Y. Miyazaki, M.M., K.N., M. Hara, M.T., S. Kai, and J.O. interpreted data and reviewed and approved the final manuscript.

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Recommended Screening and Preventive Practices for Long-term Survivors after Hematopoietic Cell Transplantation

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Abstract

Advances in hematopoietic cell transplantation (HCT) technology and supportive care techniques have led to improvements in long-term survival after HCT. Emerging indications for transplantation, introduction of newer graft sources (e.g. umbilical cord blood) and transplantation of older patients using less intense conditioning regimens have also contributed to an increase in the number of HCT survivors. These survivors are at risk for developing late complications secondary to pre-, peri- and post-transplant exposures and risk-factors. Guidelines for screening and preventive practices for HCT survivors were published in 2006. An international group of transplant experts was convened in 2011 to review contemporary literature and update the recommendations while considering the changing practice of transplantation and international applicability of these guidelines. This review provides the updated recommendations for screening and preventive practices for pediatric and adult survivors of autologous and allogeneic HCT.

Keywords

Hematopoietic cell transplantation; Allogeneic; Autologous; Late complications; Screening; Prevention

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INTRODUCTION

Approximately 50,000 people undergo hematopoietic cell transplantation (HCT) worldwide each year. Advances in transplantation techniques and supportive care practices have led to progressive improvements in survival for HCT recipients. As patients survive long-term after transplantation, they are at risk for developing late complications related to pre-, peri- and post-transplant exposures. These complications can cause substantial morbidity, impair quality of life and can contribute to late mortality in HCT recipients. Several studies have shown that the life expectancy of HCT survivors is lower than expected at 10 to 30 years post-transplantation and secondary cancers, infections and organ dysfunction are common causes of late deaths in this population.[1–6]

Recognizing the need for guidance about appropriate systematic long-term followup of HCT-survivors, the Center for International Blood and Marrow Transplant Research (CIBMTR), the European Group for Blood and Marrow Transplantation (EBMT), and the American Society of Blood and Marrow Transplantation (ASBMT) convened a group of experts in 2006 and provided consensus recommendations for screening and preventive practices for autologous and allogeneic HCT survivors.[7,8] To update these previous guidelines, the international working group was reconvened in 2011 to review the prevailing literature in late effects of transplantation and to suggest revised guidelines, if applicable. To ensure international applicability, the working group included participants from the Asia-Pacific Blood and Marrow Transplantation Group (APBMT), the Bone Marrow Transplant Society of Australia and New Zealand (BMTSANZ), the East Mediterranean Blood and Marrow Transplantation Group (EMBMT) and Sociedade Brasileira de Transplante de Medula Ossea (SBTMO).

The proposed guidelines focus on risks faced by children and adults who have survived 6 months or more following transplantation and address autologous and allogeneic HCT recipients. Since long-term HCT recipients may no longer be under the care of transplant centers and may have returned to the care of community health care providers, the guidelines are geared towards providers who routinely care for HCT recipients as well as those who do not. The National Marrow Donor Program (NMDP) publishes a patient version of the followup guidelines (www.marrow.org); we recommend that patients use these guidelines to establish a long-term followup care plan in consultation with their health care provider based on their individual exposures and risk factors.

The working group recognized the general lack of clinical trials focused on screening and preventive practices among HCT recipients and the need for more research in this area. Hence, many of these recommendations are not based on evidence derived from randomized or other controlled trials but are supported by retrospective studies that have identified specific complications in long-term survivors and their associated risk-factors. When such studies are not available, the guidelines are based on knowledge derived from non-transplant patients as well as on the consensus opinion of the working group participants. Taking into account the risks and potential consequences of late complications, they represent sensible practices to optimize outcomes. The recommendations should not be interpreted as mandatory for all recipients; good medical practice and judgment dictate that certain recommendations may not be applicable or may even be contraindicated in individual patients or groups of patients.

It was also recognized that the practice of HCT is continuously changing. Some examples of such changes include emerging indications for transplantation (e.g. autoimmune diseases, sickle cell disease), increased utilization of newer donor sources (e.g. umbilical cord blood and haploidentical donors), decreased use of total body irradiation (TBI) for conditioning

and evaluation of novel therapies as part of HCT (e.g. post-transplant maintenance therapy in myeloma). With the advent of non-myeloablative and reduced intensity conditioning (NMA/RIC) regimens, a larger number of older patients now receive transplantation. The risks and constellation of late complications may change as newer practices in transplantation become more prevalent. Providers should be cognizant of any unique exposures and risks associated with these practices (e.g. delayed immune reconstitution in umbilical cord blood recipients) when considering a long-term followup care plan for their patients.

A broad constellation of medical issues faced by late survivors of transplantation is presented. Most of the late complications discussed here pertain particularly to allogeneic recipients. However, autologous recipients are at risk for many of the same late complications and may experience unusual toxicity or immune impairment following transplantation that places them at risk similar to allogeneic recipients (e.g. exposure to prolonged corticosteroids or other drugs that may cause prolonged lymphopenia post-transplantation). Therefore, although some of the following recommendations do not generally apply to autologous recipients, providers should remain alert to these complications in all patients.

The guidelines are summarized in Tables 1 and 2. The Appendix includes tables that highlight recommendations for post-transplant immunizations (Appendix Table A) and recommendations by selected exposures/risk-factors (TBI, chronic GVHD, pediatric recipients) (Appendix Table B). Appendix Table C lists other guidelines that have been referenced in this manuscript along with current links to their website. Materials based on these guidelines will be available at the CIBMTR website (www.cibmtr.org/ReferenceCenter). Readers can also refer to guidelines developed by the Children's Oncology Group for followup for pediatric cancer survivors, which include information on pediatric HCT recipients (www.survivorshipguidelines.org). Representative references are included in this document to guide readers who would like more information on individual topics.

IMMUNITY AND INFECTIONS

International consensus guidelines for preventing infectious complications among HCT recipients were published in 2009; these guidelines comprehensively address late infectious complications of transplantation and provide recommendations for vaccination of HCT recipients.[9–11] Environmental risks, safe sex, water and food safety and travel safety among HCT recipients have also been covered by these guidelines. Patients who are immune compromised should be educated regarding their immune status and of the warning symptoms of infection and advised to seek early medical attention if they have symptoms.

Infectious complications are frequent in the period soon after HCT because of cytopenias, immune ablation and/or immunosuppression. Immune reconstitution occurs gradually over time (generally 12–18 months) and is slower for allogeneic recipients, particularly those receiving umbilical cord blood, HLA-mismatched or T-cell depleted grafts and in survivors with graft-versus-host disease (GVHD) or those who have received prolonged immunosuppression.[12] T-helper lymphocyte (CD4) counts and CD4/CD8 ratios are good markers of immune reconstitution and some experts use these assessments as surrogate markers of the completeness of immune reconstitution to guide duration of viral or other infection prophylaxis after HCT.

Bacterial, fungal, and viral infections may occur months or years after transplantation in patients with delayed immune reconstitution. Although infectious risk is highest in the first 1–2 years after transplantation, an increased risk of infection may continue long-term for

some recipients of allogeneic transplants, such as patients with chronic GVHD requiring extended immunosuppressive therapy. In patients with chronic GVHD, opsonization is impaired, and encapsulated bacteria (*N. meningitides, H. influenzae,* and *S. pneumonia*) may cause rapidly progressive and life-threatening infection. Furthermore, patients may have undergone splenectomy for the treatment of their underlying disease or may be functionally asplenic secondary to GVHD or splenic irradiation. Although patients with asplenia are at increased risk of infections, recommendations regarding antibiotic prophylaxis are inconsistent. Patients with combined risk of asplenia and immunosuppression for GVHD should receive antibiotic prophylaxis as recommended below. Otherwise patients with asplenia should, at a minimum, be warned regarding the need for prompt medical attention for febrile illnesses.

Aspergillus infection of the lungs or sinuses is the most commonly described late fungal infection although *Candida* and *Mucor* species are late pathogens seen infrequently. Late-onset cytomegalovirus (CMV) reactivation and infection has been reported more frequently in recent years with the increasing use of prophylactic or preemptive antiviral drugs in the early post-HCT period. Late CMV infections are most commonly seen in patients treated for early CMV infection or in those with chronic GVHD or late immune manipulation (e.g. donor lymphocyte infusion recipients). Varicella zoster virus (VZV) infection frequently occurs in the first year after transplantation, especially in patients with chronic GVHD. In patients receiving prophylaxis against herpes virus infections, VZV reactivation is most commonly seen in the 2–3 months after cessation of prophylaxis. Acyclovir prophylaxis is recommended for 1-year post-transplantation for both autologous and allogeneic recipients at risk for VZV disease; prophylaxis may be continued beyond 1-year among patients who have chronic GVHD or require systemic immunesuppression. Recurrent herpes simplex virus infections can occasionally occur in patients with chronic GVHD.

Although *Pneumocystis jirovecii* (previously *Pneumocystis carinii*) pneumonia (PCP) generally occurs during the first 6 months after HCT, patients are at risk for as long as immunosuppressive therapy is given for chronic GVHD. Autologous HCT recipients are also at risk of PCP, particularly during the first 6 months; the risk may be substantial if there has been prolonged corticosteroid exposure before or after transplantation and in patients who have received intensive conditioning.

Sinusitis is an occasional complication, especially after allogeneic HCT, and is more frequent in patients with low immunoglobulin levels. Sinus pathogens are rarely identified because invasive diagnostic procedures are not frequently performed. Exposure to calcineurin inhibitors that can induce mucosal hypertrophy and mucosal involvement by chronic GVHD can increase the risk of secondary sinus infections with bacteria or molds.

Supplemental intravenous immune globulin (IVIg) is sometimes recommended for patients with severe infections and IgG levels below 400 mg/dL (4 g/L) and infusions are continued until infection has abated.[9,10] The use of prophylactic IVIg in HCT patients in the absence of infection remains controversial.

Transplant recipients who reside in certain geographic areas may be susceptible to locally prevalent infections (e.g., tuberculosis, malaria, Chagas disease, leishmaniasis). Health care providers taking care of such patients should be aware of guidelines for the prevention and management of such infections.[10,13,14]

Recommendations

- Patients with chronic GVHD should receive antibiotic prophylaxis targeting encapsulated organisms given for at least as long as immunosuppressive therapy is administered.
- Antiviral and antifungal prophylaxis should be considered in patients at high risk for viral and fungal infections (e.g., patients with chronic GVHD) according to published guidelines.[9,10] Screening for CMV reactivation should be based on risk factors, including intensity of immunosuppression.
- Administration of prophylactic antibiotics for oral procedures should follow the American Heart Association guidelines for endocarditis prophylaxis.[15] Some experts recommend antibiotic prophylaxis before dental care in patients on immunosuppressive therapy for chronic GVHD and in patients with indwelling central venous catheters.
- Allogeneic HCT recipients should receive PCP prophylaxis from engraftment until at least 6 months after transplantation or as long as immunosuppressive therapy is given (e.g., for the treatment or prevention of chronic GVHD). PCP prophylaxis for 3 to 6 months post-transplantation should be considered for autologous HCT recipients with substantial immunosuppression (e.g. patients with lymphoma, leukemia or myeloma, especially when pre-transplant treatments or conditioning regimens have included purine analogues or high dose corticosteroids).
- Immunization with inactivated vaccines for all patients according to published guidelines (Appendix Table A).[9–11] Since patients with chronic GVHD can mount responses to vaccines and are at risk for infections, postponing vaccination in patients with GVHD is not recommended with the exception of live vaccines. When vaccinating patients with active GVHD, it may be prudent to measure specific antibody levels before and after vaccination, to determine their level of protection and need for booster immunizations.

OCULAR COMPLICATIONS

There are three main ocular late effects after HCT. Anterior segment ocular complications of keratoconjunctivitis sicca syndrome and cataracts are well described. Ischemic microvascular retinopathy is a posterior segment complication that is being increasingly recognized and appears to be related to radiation exposure.

Ocular sicca syndrome is usually part of a more general sicca syndrome with xerostomia, vaginitis, and dryness of skin and is associated with chronic GVHD.[16] Ocular manifestations include reduced tear flow, keratoconjunctivitis sicca, sterile conjunctivitis, corneal epithelial defects, and corneal ulceration. Symptoms include burning, irritation, pain, foreign body sensation, blurred vision, photophobia, and paradoxically, excessive tearing. The diagnosis of keratoconjunctivitis sicca is made by the presence of appropriate symptoms, evidence of decreased tear production on Schirmer's test, and clinical signs of keratitis. In all cases, infectious keratitis must be ruled out. The incidence is approximately 40–60% in patients with chronic GVHD.[17] Artificial tears can provide symptomatic treatment of dry eye. Information regarding frequency of use of artificial tear drops can indicate severity of dry eye syndrome. Treatment includes systemic treatment of chronic GVHD and topical treatment to increase lubrication, control evaporation or drainage, and decrease ocular surface inflammation.[18] Temporary or permanent occlusion of the tear-duct puncta for drainage control may provide benefit. In general, contact lens usage is discouraged in patients with keratoconjunctivitis sicca because of an increased risk of abrasion: however,

some lenses such as scleral lenses may be beneficial in severe cases to control evaporation. Such an approach should occur only with the close supervision of an ophthalmologist. Topical corticosteroids or calcineurin inhibitors may improve symptoms but can cause sight-threatening complications when inappropriately used in herpes simplex virus or bacterial keratitis. Ocular surface inflammation may be decreased with autologous serum, but this treatment is available in a limited number of centers.

Cataract formation occurs frequently after TBI exposure. After myeloablative single-dose TBI, almost all patients develop cataracts within three to four years. Fractionation of TBI delays onset and reduces the incidence of cataract to 40–70% at ten years post-transplant.[19,20] In patients conditioned without TBI, the probability of cataract formation at 10 years is 5–20%.[20,21] Other risk factors for cataract formation after HCT are older age, use of corticosteroids, and allogeneic compared to autologous transplantation. Approximately 45% of recipients treated with corticosteroids for a prolonged period of time develop cataracts at 10 years. In the near future, the overall cumulative incidence of cataracts after HCT is expected to decrease as fewer patients receive TBI based conditioning. Cataracts are effectively treated surgically. Cataract extraction can be performed safely even when ocular sicca is present. Surgery is indicated if vision is impaired and the impairment is interfering with daily life.

Ischemic microvascular retinopathy presents with cotton-wool spots and optic-disc edema. Retinopathy is observed almost exclusively after allogeneic transplantation, particularly in patients conditioned with TBI and in patients receiving cyclosporine for GVHD prophylaxis. In most cases, retinal lesions resolve with withdrawal or reduction of immunosuppressive therapy, even in cases where visual acuity is decreased. Other ocular complications in the posterior segment include hemorrhage, optic disc edema, and infectious retinitis (e.g., from herpes viruses including CMV, toxoplasma, and fungi).

Recommendations

- Routine clinical evaluation of visual history and symptoms, with attention to sicca syndrome, is recommended at 6 months, 1 year and yearly thereafter for all HCT recipients.
- Referral to an expert in ophthalmology for routine ocular examination with measurement of visual acuity and fundus examination at 1 year after transplant is recommended for all HCT recipients. Patients with chronic GVHD may be referred for ophthalmologic exam sooner than 1 year post-transplant. Subsequent frequency of routine screening should be individualized according to recognized defects, ocular symptoms or the presence of chronic GVHD.
- Patients experiencing visual symptoms should undergo ocular examination immediately.

ORAL COMPLICATIONS

Late complications involving the oral cavity are common after HCT. The most important risk factors for oral late effects are oral chronic GVHD, the use and dose of irradiation to head and neck region, underlying diagnosis of Fanconi's anemia and the age of the patient at HCT. Pre-transplant evaluation should include clinical assessment of oral health status to serve as a baseline for monitoring post-transplant oral complications.

The mouth is one of the most frequently affected organs in chronic GVHD.[22,23] The oral changes involving the oral mucosa, salivary glands, oral and lingual muscles, taste buds and gingiva may completely regress, but some long term sequela may continue despite the

resolution of chronic GVHD. Patients often report oral pain, dryness, odynophagia, dysphagia and sensitivity (irritation from normally tolerated spices, foods, liquids or flavors) that may limit oral intake. The presence of lichen planus, hyperkeratotic plaques and restriction of mouth opening by peri-oral fasciitis or skin sclerosis are diagnostic signs of oral GVHD. Patients may also have mucosal erythema, atrophy, oral dryness, mucoceles (due to inflammation and obstruction of the salivary gland ducts), pseudomembranes and ulcers. Salivary gland dysfunction and xerostomia increase the risk of dental caries, periodontal disease and oral cancer.[22,24] Patients with GVHD can be treated with topical oral steroids, systemic treatments for GVHD, and supportive care for xerostomia symptoms as outlined below.

Even in patients who have never had GVHD, some degree of salivary gland hypofunction may persist for prolonged periods of time after receiving chemotherapy, and especially after local irradiation. Oral dryness is also a side effect of commonly used medications (e.g. antidepressants, anti-histamines, diuretics, muscle relaxants and some analgesics). Medication lists should be reviewed to identify and eliminate any drugs that can cause or exacerbate xerostomia. Depending on the severity of xerostomia, patients may complain of oral sensitivity, abnormal taste and may feel a constant sore throat, or have problems speaking and swallowing. The decrease in salivation predisposes patients to dental decay, oral infections (e.g. herpes simplex and oral candidiasis), mechanical and epithelial injuries, and impairs re-mineralization of teeth. Xerostomia can be difficult to manage. Symptom relief can be achieved with artificial saliva and oral rinses; sugar-free candies or gum can stimulate the saliva flow. Sialogogues (e.g. pilocarpine, cevimeline) may be tried in adults. Frequent sipping of water may help decrease symptoms, and especially help chewing and swallowing food. Patients with xerostomia should receive meticulous oral hygiene, undertake preventive measures for dental and periodontal disease, and aggressive treatment of oral infections. Further trauma to the oral mucosa should be avoided and mouth-guards may be used, if necessary. Oral piercing should be avoided.

Squamous cell oral cancer can arise from the buccal mucosa, salivary glands, gingiva, lip or tongue (see section on Secondary Cancers).[24–26] Patients with a history of oral chronic GVHD and patients with Fanconi's anemia are particularly at risk and must be carefully screened throughout their lives. Frequent self and professional oral examination is the mainstay for early diagnosis of oral cancer. Patients should be vigilant for and report lesions that do not heal, leukoplakia, localized pain and changes in color or texture of the mucosa. Patients with Fanconi's anemia should be examined every six months and oral examination should be part of the standard annual examination of all other HCT patients.

Children undergoing HCT may have damage to the enamel layer and the teeth may have discolored patches or stain easily. Depending on the child's age, permanent teeth may start developing again within a few months of transplantation. Normal dental development may be altered in 50%–80% of children due to prior therapies or conditioning regimen exposure.[27] Tooth agenesis, hypodontia, microdontia of the crowns of erupted permanent teeth, narrowing of the pulp canal, thinning and tapering of the roots of erupted permanent molars or incisors, delayed eruption and primary tooth retention have been described and may jeopardize occlusal development. After irradiation, underdevelopment of the mandible and anomalies in the mandibular joint may also occur. Young age at HCT and exposure to TBI are important risk factors for problems with dental development.

Among HCT recipients who require dental procedures, the American Heart Association recommendations for antimicrobial prophylaxis against endocarditis should be followed (see section on Immunity and Infections).[15]