

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

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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 (eg, 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 posttransplantation exposures and risk factors. Guidelines for screening and preventive practices for HCT survivors were published in 2006. An international group of transplantation 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.

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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 posttransplantation 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

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expectancy of HCT survivors is lower than expected at 10 to 30 years posttransplantation 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 follow-up of HCT survivors, the Center for International Blood and Marrow Transplant Research (CIBMTR), the European Group for Blood and Marrow Transplantation, and the American Society for Blood and Marrow Transplantation 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, the Bone Marrow Transplant Society of Australia and New Zealand, the East Mediterranean Blood and Marrow Transplantation Group, and Sociedade Brasileira de Transplante de Medula Ossea.

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 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 Supplementary Tables 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. 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.

The National Marrow Donor Program (NMDP) publishes a patient version of the followup guidelines (www.BeTheMatch.org/Patient); 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 NMDP also makes a summary of the guidelines available for physicians, (online, mobile app, and in print at www.marlow.org/md-guidelines).

Table 1. Summary Recommendations for Screening and Prevention of Late Complications in Long-Term HCT Survivors

Tissues/Organs	Late Complications	General Risk Factors	Monitoring Tests	Monitoring Tests and Preventive Measures on All HCT Recipients	Monitoring Tests and Preventive Measures in Special Populations
Immune system	-Infections	-Donor source -HLA disparity -T cell depletion -GVHD -Prolonged immunosuppression -Venous access devices	-CMV antigen or PCR in patients at high risk for CMV reactivation	-PCP prophylaxis for initial 6 months after HCT -Immunizations posttransplantation according to published guidelines -Administration of antibiotics for endocarditis prophylaxis according to American Heart Association guidelines	-Patients with cGVHD: Antimicrobial prophylaxis targeting encapsulated organisms and PCP for the duration of immunosuppressive therapy -Patients with cGVHD: Screening for CMV reactivation should be based on risk factors, including intensity of immunosuppression.
Ocular	-Cataracts -Sicca syndrome -Microvascular retinopathy	-TBI/radiation exposure to head and neck -Corticosteroids -GVHD	-Ophthalmologic exam	-Routine clinical evaluation at 6 months and 1 year after HCT and at least yearly thereafter -Ophthalmologic examination with measurement of visual acuity and fundus examination at 1 year after HCT, subsequent evaluation based on findings and risk factors -Prompt ophthalmologic examination in patients with visual symptoms	-Patients with cGVHD: Routine clinical evaluation, and if indicated, ophthalmologic examination more frequently
Oral	-Sicca syndrome -Caries	-GVHD -TBI/radiation exposure to head and neck	-Dental assessment	-Education about preventive oral health practices -Clinical oral assessment at 6 months and 1 year after HCT and at least yearly thereafter with particular attention to intraoral malignancy evaluation -Dental assessment at 1 year after HCT and then at least yearly thereafter	-Pediatric recipients: Yearly assessment of teeth development -Patients with cGVHD: Consider more frequent oral and dental assessments with particular attention to intraoral malignancy evaluation
Respiratory	-Idiopathic pneumonia syndrome -Bronchiolitis obliterans syndrome -Cryptogenic organizing pneumonia -Sinopulmonary infections	-TBI/radiation exposure to chest -GVHD -Infectious agents -Allogeneic HCT -Busulfan exposure	-PFTs -Radiologic studies (eg, chest x-ray, CT scan)	-Routine clinical evaluation at 6 months and 1 year after HCT and at least yearly thereafter -Assessment of tobacco use and counselling against smoking -PFTs and focused radiologic assessment for allogeneic HCT recipients with symptoms or signs of lung compromise	-Patients with cGVHD: Some experts recommend earlier and more frequent clinical evaluation and PFTs
Cardiac and vascular	-Cardiomyopathy -Congestive heart failure -Arrhythmias -Valvular anomaly -Coronary artery disease -Cerebrovascular disease -Peripheral arterial disease	-Anthracycline exposure -TBI/radiation exposure to neck or chest -Older age at HCT -Allogeneic HCT -Cardiovascular risk factors before/after HCT -Chronic kidney disease -Metabolic syndrome	-Cumulative dose of anthracyclines -Echocardiogram with ventricular function, ECG in patients at risk and in symptomatic patients -Fasting lipid profile (including HDL-C, LDL-C and triglycerides) -Fasting blood sugar	-Routine clinical assessment of cardiovascular risk factors as per general health maintenance at 1 year and at least yearly thereafter -Education and counseling on "heart-healthy" lifestyle (regular exercise, healthy weight, no smoking, dietary counseling) -Early treatment of cardiovascular risk factors such as diabetes, hypertension, and dyslipidemia -Administration of antibiotics for endocarditis prophylaxis according to American Heart Association guidelines	

Liver	<ul style="list-style-type: none"> -GVHD -Hepatitis B -Hepatitis C -Iron overload 	<ul style="list-style-type: none"> -Cumulative transfusion exposure -Risk factors for viral hepatitis transmission 	<ul style="list-style-type: none"> -LFTs -Liver biopsy -Serum ferritin -Imaging for iron overload (MRI or SQUID) 	<ul style="list-style-type: none"> -LFTs every 3-6 months in the first year, then individualized, but at least yearly thereafter -Monitor viral load by PCR for patients with known hepatitis B or C, with liver and infectious disease specialist consultation -Consider liver biopsy at 8-10 years after HCT to assess cirrhosis in patients with chronic HCV infection -Serum ferritin at 1 year after HCT in patients who have received RBC transfusions; consider liver biopsy or imaging study for abnormal results based on magnitude of elevation and clinical context; subsequent monitoring is suggested for patients with elevated LFTs, continued RBC transfusions, or presence of HCV infection 	
Renal and genitourinary	<ul style="list-style-type: none"> -Chronic kidney disease -Bladder dysfunction -Urinary tract infections 	<ul style="list-style-type: none"> -TBI -Drug exposure (eg, calcineurin inhibitors, amphotericin, aminoglycosides) -CMV -Hemorrhagic cystitis 	<ul style="list-style-type: none"> -Urine protein -Serum creatinine -BUN 	<ul style="list-style-type: none"> -Blood pressure assessment at every clinic visit, with aggressive hypertension management -Assess renal function with BUN, creatinine and urine protein at 6 months, 1 year and at least yearly thereafter -Consider further workup (kidney biopsy or renal ultrasound) for further workup of renal dysfunction as clinically indicated 	
Muscle and connective tissue	<ul style="list-style-type: none"> -Myopathy -Fascitis/scleroderma -Polymyositis 	<ul style="list-style-type: none"> -Corticosteroids -GVHD 	<ul style="list-style-type: none"> -Evaluate ability to stand from a sitting position -Clinical evaluation of joint range of motion 	<ul style="list-style-type: none"> -Follow general population guidelines for physical activity -Frequent clinical evaluation for myopathy in patients on corticosteroids 	<ul style="list-style-type: none"> -Patients with cGVHD: Physical therapy consultation in patients with prolonged corticosteroid exposure, fascitis, or scleroderma -Patients with cGVHD: Frequent clinical evaluation by manual muscle tests or by assessing ability to go from sitting to standing position for patients on prolonged corticosteroids
Skeletal	<ul style="list-style-type: none"> -Osteopenia/osteoporosis -Avascular necrosis 	<ul style="list-style-type: none"> -Inactivity -TBI -Corticosteroids -GVHD -Hypogonadism -Allogeneic HCT 	<ul style="list-style-type: none"> -Dual photon densitometry -MRI to evaluate patients with joint symptoms 	<ul style="list-style-type: none"> -Dual photon densitometry at 1 year for adult women, all allogeneic HCT recipients and patients who are at high risk for bone loss; subsequent testing determined by defects or to assess response to therapy -Physical activity, vitamin D, and calcium supplementation to prevent loss of bone density 	<ul style="list-style-type: none"> -Patients with cGVHD: Consider dual photon densitometry at an earlier date in patients with prolonged corticosteroid or calcineurin inhibitor exposure.
Nervous system	<ul style="list-style-type: none"> -Leukoencephalopathy -Late infections -Neuropsychological and cognitive deficits -Calcineurin neurotoxicity -Peripheral neuropathy 	<ul style="list-style-type: none"> -TBI/radiation exposure to head -GVHD -Exposure to fludarabine -Intrathecal chemotherapy 	-	<ul style="list-style-type: none"> -Clinical evaluation for symptoms and signs of neurologic dysfunction at 1 year and yearly thereafter -Diagnostic testing (eg, radiographs, nerve conduction studies) for those with symptoms or signs 	<ul style="list-style-type: none"> -Pediatric recipients: Annual assessment for cognitive development milestones

(Continued)

Table 1. (Continued)

Tissues/Organs	Late Complications	General Risk Factors	Monitoring Tests	Monitoring Tests and Preventive Measures on All HCT Recipients	Monitoring Tests and Preventive Measures in Special Populations
Endocrine	-Hypothyroidism -Hypoadrenalism -Hypogonadism -Growth retardation	-TBI/radiation exposure (eg, head and neck, CNS) -Corticosteroids -Young age at HCT -Chemotherapy exposure	-Thyroid function tests -FSH, LH, testosterone -Growth velocity in children	-Thyroid function testing yearly post-HCT, or if relevant symptoms develop -Clinical and endocrinologic gonadal assessment for postpubertal women at 1 year; subsequent follow-up based on menopausal status -Gonadal function in men, including FSH, LH, and testosterone, should be assessed as warranted by symptoms	-Pediatric recipients: Clinical and endocrinologic gonadal assessment for prepubertal boys and girls within 1 year of transplantation, with further follow-up as determined in consultation with a pediatric endocrinologist -Pediatric recipients: Monitor growth velocity in children annually; assessment of thyroid and growth hormone function if clinically indicated -Patients with cGVHD: Slow terminal tapering of corticosteroids for those with prolonged exposure -Patients with cGVHD: Consider stress doses of corticosteroids during acute illness for patients who have received chronic corticosteroids
Mucocutaneous	-Cutaneous sclerosis -Genital GVHD	-GVHD -TBI/radiation exposure to pelvis	-Pelvic exam	-Counsel patients to perform routine self-exam of skin and avoid excessive exposure to sunlight without adequate protection -Annual gynecologic exam in women to detect early involvement of vaginal mucosa by GVHD	-Patients with cGVHD and TBI recipients: Consider more frequent gynecologic evaluation based on clinical symptoms
Second cancers	-Solid tumors -Hematologic malignancies -PTLD	-GVHD -TBI/radiation exposure -T cell depletion -Exposure to alkylating agents or etoposide	-Mammogram -Screening for colon cancer (eg, colonoscopy, sigmoidoscopy, fecal occult blood testing) -Pap smear	-Counsel patients about risks of secondary malignancies annually and encourage them to perform self-exam (eg, skin, testicles/genitalia) -Counsel patients to avoid high-risk behaviors (eg, smoking) -Follow general population recommendations for cancer screening	-Patients with cGVHD: Clinical and dental evaluation with particular attention toward oral and pharyngeal cancer -TBI and chest irradiation recipients: Screening mammography in women starting at age 25 or 8 years after radiation exposure, whichever occurs later but no later than age 40
Psychosocial and sexual	-Depression -Anxiety -Fatigue -Sexual dysfunction	-Prior psychiatric morbidity -Hypogonadism	-Psychological evaluation	-Clinical assessment throughout recovery period, at 6 months, 1 year, and annually thereafter, with mental health professional counseling recommended for those with recognized deficits -Encouragement of robust support networks -Regularly assess level of spousal/caregiver psychological adjustment and family functioning -Query adults about sexual function at 6 months, 1 year, and at least annually thereafter	
Fertility	-Infertility	-TBI/radiation exposure -Chemotherapy exposure	-FSH, LH levels	-Consider referral to appropriate specialists for patients who are contemplating a pregnancy or are having difficulty conceiving -Counsel sexually active patients in the reproductive age group about birth control post-HCT	
General health				-Recommended screening as per general population (see text)	

PCR, polymerase chain reaction; PCP, Pneumocystis pneumonia; CT, computed tomography; ECG, electrocardiogram; BUN, blood urea nitrogen; CNS, central nervous system; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

Table 2. Abbreviated Summary Recommendations for Screening and Prevention of Late Complications in Long-Term HCT Survivors Organized by Time after Transplantation

Recommended Screening/Prevention	6 Months	1 Year	Annually
Immunity			
Encapsulated organism prophylaxis	2	2	2
PCP prophylaxis	1	2	2
CMV testing	2	2	2
Immunizations	1	1	1
Ocular			
Ocular clinical symptom evaluation	1	1	1
Ocular fundus exam	+	1	+
Oral complications			
Clinical assessment	1	1	1
Dental assessment	+	1	1
Respiratory			
Clinical pulmonary assessment	1	1	1
Smoking tobacco avoidance	1	1	1
Pulmonary function testing	+	+	+
Chest radiography	+	+	+
Cardiac and vascular			
Cardiovascular risk-factor assessment	+	1	1
Liver			
Liver function testing	1	1	+
Serum ferritin testing		1	+
Kidney			
Blood pressure screening	1	1	1
Urine protein screening	1	1	1
BUN/creatinine testing	1	1	1
Muscle and connective tissue			
Evaluation for muscle weakness	2	2	2
Physical activity counseling	1	1	1
Skeletal			
Bone density testing (adult women, all allogeneic transplantation recipients and patients at high risk for bone loss)		1	+
Nervous system			
Neurologic clinical evaluation	+	1	1
Evaluate for cognitive development		1	1
Endocrine			
Thyroid function testing		1	1
Growth velocity in children		1	1
Gonadal function assessment (prepubertal men and women)	1	1	1
Gonadal function assessment (postpubertal women)		1	+
Gonadal function assessment (postpubertal men)		+	+
Mucocutaneous			
Skin self-exam and sun exposure counseling	1	1	1
Gynecologic exam in women	+	1	1
Second cancers			
Second cancer vigilance counseling		1	1
Screening for second cancers		1	1
Psychosocial			
Psychosocial/QOL clinical assessment	1	1	1
Sexual function assessment	1	1	1

1 = recommended for all transplantation recipients; 2 = recommended for any patient with ongoing cGVHD or immunosuppression; + = reassessment recommended for abnormal testing in a previous time period or for new signs/symptoms.

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 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 to 2 years after transplantation, an increased risk of infection may continue long term for some recipients of allogeneic transplantations, such as patients with cGVHD requiring extended immunosuppressive therapy. In patients with cGVHD, 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 in the information to follow. 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 cGVHD or late immune manipulation (eg, donor lymphocyte infusion recipients). Varicella zoster virus (VZV) infection frequently occurs in the first year after transplantation,

especially in patients with cGVHD. In patients receiving prophylaxis against herpes virus infections, VZV reactivation is most commonly seen in the 2 to 3 months after cessation of prophylaxis. Acyclovir prophylaxis is recommended for 1-year posttransplantation for both autologous and allogeneic recipients at risk for VZV disease; prophylaxis may be continued beyond 1 year among patients who have cGVHD or require systemic immune suppression. Recurrent herpes simplex virus infections can occasionally occur in patients with cGVHD.

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 cGVHD. 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 cGVHD can increase the risk of secondary sinus infections with bacteria or molds.

Supplemental intravenous immune globulin 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 intravenous immune globulin in HCT patients in the absence of infection remains controversial.

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

Recommendations

1. Patients with cGVHD should receive antibiotic prophylaxis targeting encapsulated organisms given for at least as long as immunosuppressive therapy is administered.
2. Antiviral and antifungal prophylaxis should be considered in patients at high risk for viral and fungal infections (eg, patients with cGVHD) according to published guidelines [9,10]. Screening for CMV reactivation should be based on risk factors, including intensity of immunosuppression.

3. 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 cGVHD and in patients with indwelling central venous catheters.
4. Allogeneic HCT recipients should receive PCP prophylaxis from engraftment until at least 6 months after transplantation or as long as immunosuppressive therapy is given (eg, for the treatment or prevention of cGVHD). PCP prophylaxis for 3 to 6 months posttransplantation should be considered for autologous HCT recipients with substantial immunosuppression (eg, patients with lymphoma, leukemia, or myeloma, especially when pretransplantation treatments or conditioning regimens have included purine analogues or high-dose corticosteroids).
5. Immunization with inactivated vaccines for all patients according to published guidelines (Appendix Table A) [9-11]. Because patients with cGVHD 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 cGVHD [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% to 60% in patients with cGVHD [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 cGVHD 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 3 to 4 years. Fractionation of TBI delays onset and reduces the incidence of cataract to 40% to 70% at 10 years posttransplantation [19,20]. In patients conditioned without TBI, the probability of cataract formation at 10 years is 5% to 20% [20,21]. Other risk factors for cataract formation after HCT are older age, use of corticosteroids, and allogeneic compared with 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.

Patients with ischemic microvascular retinopathy present 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 (eg, from herpes viruses including CMV, toxoplasma, and fungi).

Recommendations

1. 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.
2. Referral to an expert in ophthalmology for routine ocular examination with measurement of visual acuity and fundus examination at 1 year after transplantation is recommended for all HCT recipients. Patients with cGVHD may be referred for an ophthalmologic exam sooner than 1 year posttransplantation. Subsequent frequency of routine screening should be individualized according to recognized defects, ocular symptoms, or the presence of cGVHD.
3. 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 cGVHD, 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. Pretransplantation evaluation should include clinical assessment of oral health status to serve as a baseline for monitoring posttransplantation oral complications.

The mouth is one of the most frequently affected organs in cGVHD [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 cGVHD. 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 perioral fasciitis or skin sclerosis are diagnostic signs of oral GVHD. Patients may also have mucosal erythema, atrophy, oral dryness, mucoceles (because of 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 in the information to follow.

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 (eg, antidepressants, antihistamines, 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 (eg, herpes simplex and oral candidiasis), mechanical and epithelial injuries, and impairs remineralization 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 (eg, 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 cGVHD 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 6 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% to 80% of children because of 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].

Recommendations

1. All HCT recipients should be educated about preventive oral health and routine dental maintenance. Patients should also be counseled to avoid smoking and chewing tobacco, decrease regular intake of sugar containing beverages, and avoid intraoral piercing.
2. Clinical oral evaluations should be performed at 6 months, 1 year, and yearly thereafter. More frequent evaluations may be needed in patients at high risk of oral complications (eg, cGVHD, exposure to TBI). Monitoring of oral complications posttransplantation is facilitated by thorough pre-HCT baseline oral assessment.
3. Patients at high risk for squamous cell cancers of the oral cavity (eg, oral cGVHD, Fanconi's anemia) should undergo clinical oral evaluations every 6 months and should be educated to maintain meticulous oral hygiene and taught oral self-inspection.
4. All HCT recipients should receive a thorough evaluation by a dentist or oral medicine specialist at 1 year after HCT and yearly thereafter. More frequent dental consultations may be considered in patients with oral GVHD or Fanconi's anemia. At each visit, it is important to check for a history of xerostomia and high-risk habits and to perform a thorough oral, head, and neck and dental exam. Appropriate dental and radiologic assessment for tooth development should be performed in children.

RESPIRATORY COMPLICATIONS

Late pulmonary complications among HCT recipients include idiopathic pneumonia syndrome, bronchiolitis obliterans syndrome (BOS), cryptogenic organizing pneumonia (COP), and sinopulmonary infections [28]. Allogeneic HCT recipients have higher risks than autologous HCT recipients. Predisposing factors can include infections, extent, and type of pretransplantation and conditioning regimen chemotherapy and radiation exposure, and GVHD. Pulmonary complications can be associated with significant morbidity and mortality.

Idiopathic pneumonia syndrome, also known as *interstitial pneumonitis*, more commonly presents in the early posttransplantation period. However, it can occur in long-term survivors and can lead to late respiratory impairment. Predisposing factors include allogeneic HCT, exposure to high-dose TBI, and GVHD. Immune compromise delays recovery from infection, allowing greater damage to the lung interstitium. Certain chemotherapeutic agents (eg, BCNU, bleomycin, busulfan, methotrexate) can cause lung toxicity directly or can enhance the damaging effects

of radiation. Fractionation of radiation and lung shielding can decrease radiation toxicity. Prophylaxis strategies focus on decreasing the risks of infections post-HCT, especially among patients with cGVHD.

BOS occurs in 2% to 14% of allogeneic HCT recipients and is almost exclusively seen among patients with cGVHD; some experts classify BOS as pulmonary GVHD [29-31]. BOS may develop in patients with no other clinical manifestations of GVHD. BOS is characterized by the new onset of an obstructive lung defect and clinically manifests as dyspnea on exertion, cough, or wheezing. Patients may be asymptomatic early in the disease process. BOS is clinically diagnosed when all of the following criteria are met together with active cGVHD in at least one organ other than the lung: (1) forced expiratory volume in 1 second (FEV₁)/forced vital capacity ratio < 0.7 and FEV₁ < 75% of predicted; (2) evidence of air trapping or small airway thickening or bronchiectasis on high-resolution chest computed tomography, residual volume >120%, or pathologic confirmation of constrictive bronchiolitis; and (3) absence of infection in the respiratory tract, documented with investigations (eg, bronchoalveolar lavage) directed by clinical symptoms. Some experts consider a decrease in the FEV₁ of 10% or greater from pretransplantation baseline as a diagnostic criterion for BOS or an indication for more frequent follow-up pulmonary function test (PFT) assessments. The value of using spirometry to screen for BOS in the absence of symptoms is not well defined. Treatment of BOS includes immunosuppressive agents such as corticosteroids, calcineurin inhibitors, sirolimus, and antithymocyte globulin. The prognosis of BOS is poor, and 5-year survival rates are <20% if patients do not respond to initial treatment [30,31].

COP, previously known as *bronchiolitis obliterans organizing pneumonia*, is a clinicopathologic syndrome that involves the bronchioles, alveolar ducts, and the alveoli, and is the result of a variety of toxic, immunologic, or inflammatory injuries to the lungs. COP presents typically in the first 6 to 12 months posttransplantation, although later onset may occur, especially in patients with cGVHD. Clinical presentation includes nonproductive cough, low-grade fevers, and dyspnea. Radiologic imaging may reveal patchy consolidation with ground glass or nodular infiltrates. Pulmonary function tests typically show a restrictive pattern. Biopsy may be needed to confirm the diagnosis of COP. Mainstay of treatment is corticosteroids, and 80% of patients can be expected to recover, but relapses are common if steroids are rapidly tapered. This complication is rare after transplantation, and no specific screening tests are available for early diagnosis and prevention.

Recurrent sinopulmonary infections can occur in patients with delayed immune reconstitution and

cGVHD (see section on Immunity and Infections). Appropriate vaccination is recommended, and in patients with ongoing immune deficiency and infections, monitoring of immune globulin levels should be considered with targeted replacement as recommended elsewhere in these guidelines.

Other rare late complications involving the lungs include diffuse alveolar hemorrhage, pulmonary thromboembolism, pulmonary veno-occlusive disease, and pleural effusions.

Recommendations

1. Routine clinical assessment by history and physical exam for pulmonary complications is recommended for all patients at 6 months, 1 year, and yearly thereafter.
2. Some experts recommend earlier and more frequent clinical assessments including PFTs in patients with cGVHD.
3. History of smoking should be assessed, and patients who smoke or are at risk for passive smoking should be counseled regarding smoking cessation.
4. In patients with symptoms or signs of lung compromise, PFTs and focused radiologic assessment should be performed as clinically indicated. Follow-up evaluations should be guided by clinical circumstances for patients with recognized defects.

CARDIAC AND VASCULAR COMPLICATIONS

In comparison to other complications, clinically evident cardiac and cardiovascular complications after HCT are rare. Cardiac toxicity accounts for late deaths in 2% of autologous and 3% of allogeneic HCT recipients. However, it is likely that cardiac and vascular complications are still underestimated. Experiences of cancer survivorship in the nontransplantation setting may provide an estimate of the magnitude of risk in HCT recipients. In a cohort of 1,474 long-term survivors with Hodgkin lymphoma (among whom 84% received mediastinal radiation), the risk of cardiac and cardiovascular diseases was three to five times increased compared with a general population [32]. Therefore, cardiac and cardiovascular complications may increase with longer follow-up after HCT.

Late cardiac events can appear years and even decades after HCT and may manifest as subclinical abnormalities or present as overt congestive heart failure or angina. The cardiac complications include any cardiac dysfunction because of cardiomyopathy, valvular anomaly, or conduction anomaly. Many factors are involved, such as the cumulative exposure to anthracyclines and chest radiation before HCT, cardiac function before transplantation, intensity and

type of conditioning regimen used, as well as post-transplantation factors. Previous use of cardiotoxic chemotherapy and chest radiation plays a major role. For patients with nonmalignant diseases such as hemoglobinopathy or aplastic anemia, transfusion history and the resultant iron overload may be important. With advancing age at the time of HCT, common pre-existing cardiac diseases may be increased. Assessment before transplantation for all HCT recipients should include inquiry about exposure to pretransplantation chemotherapy (eg, cumulative dose of anthracyclines) and chest and neck radiation therapy and evaluation of preexisting cardiac and cardiovascular disease.

Anthracycline cardiomyopathy is characterized by a dose-dependent progressive decrease in systolic left ventricular function. At total doses of <400 mg/m² body surface area, the incidence of congestive heart failure is 0.14%; this incidence increases to 7% at a dose of 550 mg/m² and to 18% at a dose of 700 mg/m². Mediastinal radiotherapy applied before HCT can cause a variety of cardiac complications by producing inflammation and fibrosis of all structures of the heart. Restrictive cardiomyopathy, fibrosis of the electrical conduction pathways with arrhythmias, and autonomic dysfunction, as well as valvular defects, with left-sided valve regurgitation and valve thickening are the deleterious consequences.

Cardiovascular disease involves changes of the whole arterial vascular network and can include cerebrovascular disease, ischemic heart disease, and peripheral arterial disease after HCT. These cardiovascular events may have diverse clinical manifestations, such as stroke, transient ischemic attack, myocardial infarction, angina pectoris, chronic coronary artery disease, ischemic leg pain, or gangrene.

In a retrospective single-center study, the cumulative incidence of a cardiovascular complication was 22% at 25 years after allogeneic HCT [33]. The relative risk of developing a late arterial event was significantly higher after allogeneic than after autologous HCT, supporting the hypothesis that the allo-reaction may be involved in the atherosclerotic process. The established cardiovascular risk factors (hypertension, dyslipidemia, diabetes, smoking, physical inactivity) were associated with higher risks of cardiovascular complications posttransplantation. Some conditioning regimens may have inherent cardiac toxicity with long-term cardiac consequences [34].

A high prevalence of metabolic syndrome, elevated triglycerides, elevated blood pressure, abdominal obesity, and diabetes has been reported among allogeneic HCT survivors, even when off immunosuppressive treatment. Prolonged and intensified immunosuppressive treatment, posttransplantation endocrine dysfunction, and insulin and/or leptin resistance could be some of the possible causes. Although studies supporting evidence-based guidelines are lacking in HCT,

prevention and early treatment of the cardiovascular risk factors may decrease the risk of late cardiovascular complications after HCT [35].

Recommendations

1. Routine clinical assessment and cardiovascular risk factor evaluation for all HCT recipients at 1 year and yearly thereafter. More frequent assessments and if clinically appropriate, extended cardiac evaluations (eg, electrocardiogram, echocardiogram) may be indicated in patients at high risk for cardiac complications (eg, patients with Hodgkin lymphoma who have received mediastinal radiation therapy, patients with amyloidosis, and patients with preexisting cardiac and vascular abnormalities).
2. Education and counseling on “heart-healthy” lifestyle (regular exercise, maintaining healthy weight, no smoking, dietary counseling) for all HCT recipients (see section on General Screening and Preventive Health).
3. Appropriate treatment of cardiovascular risk factors such as diabetes, hypertension, and dyslipidemia for all HCT recipients. Among patients started on drug therapy for dyslipidemia, follow-up assessments should be performed based on published guidelines (fasting lipid panel every 6-8 weeks until treatment goal is achieved and then every 4-6 months) [36].
4. Endocarditis prophylaxis in HCT recipients according to the recommendations of the American Heart Association [15].

LIVER COMPLICATIONS

Late liver complications are most commonly related to medications, cGVHD, hepatitis B or C virus (HCV), or iron overload [37]. The etiology of liver dysfunction may be multifactorial, and a careful history, physical examination, and review of medications can often provide clues. In addition, the time course of onset and pattern of liver function test (LFT) abnormalities, history of pretransplantation hepatitis, diagnosis of GVHD at other sites, and number of blood transfusions pre- and posttransplantation can be useful in determining the etiology of liver disease.

Chronic GVHD is a major cause of liver dysfunction after transplantation and can manifest with elevations of serum alanine transaminase, alkaline phosphatase, and gamma glutamyl transferase. Evaluation should exclude other causes of liver dysfunction (eg, viral infections, drug injury). Liver biopsy should be performed to confirm the diagnosis when liver dysfunction occurs as the only manifestation of cGVHD and systemic immunosuppression is being considered. Immunosuppressive therapy is indicated for liver

cGVHD; ursodeoxycholic acid may be used as an adjunct. Liver transplantation has successfully been performed in several rare cases of progressive liver failure [38].

Long-term survivors with hepatitis B generally have mild to moderate liver disease. Chronic HCV infection is often asymptomatic with fluctuating transaminase levels as the only manifestation during the first decade following transplantation. However, the cumulative incidence of HCV progressing to cirrhosis is 11% at 15 years and 24% at 20 years, being more rapid in transplantation than nontransplantation patients (18 versus 40 years) [39]. Extrahepatic HCV disease and genotype 3 are associated with progression to cirrhosis. In patients with known HCV infection, liver biopsy can be considered at 8 to 10 years after transplantation to assess for the presence of cirrhosis.

HCT recipients are at risk of developing iron overload primarily from red blood cell (RBC) transfusions as part of their supportive care both pre- and posttransplantation, although increased iron absorption because of ineffective erythropoiesis and a carrier state for hereditary hemochromatosis, if present, may also contribute [40]. Iron overload in late survivors has been associated with increased infections and may mimic hepatic cGVHD. Although serum ferritin is a sensitive test for iron load, as an acute phase reactant, it is not a specific test. When iron overload is suspected, the hepatic iron content should be estimated by appropriate imaging (specialized magnetic resonance imaging [MRI] protocols or superconducting quantum interference device [SQUID]) or liver biopsy. MRI and SQUID are noninvasive tests and have been shown to be sensitive and specific for quantifying liver iron content. These are the preferred methods unless a tissue sample is needed to assess for other potential etiologies of liver dysfunction. Survivors with mild iron overload may not require any therapy, as there are reports of iron load decreasing with time, but they should be counseled to avoid iron supplements and alcohol ingestion. Although more data are needed to determine the incidence of end-organ damage from iron overload, patients with significant iron overload (eg, >7 mg/g dry weight liver iron) and liver dysfunction are candidates for phlebotomy or iron-chelation therapy. Iron-chelation therapy before or early posttransplantation is being investigated in patients with pretransplantation iron overload. Among patients who are at risk for iron overload and require vitamin supplementation, iron-free preparations should be considered.

HCT recipients who have thalassemia or have been heavily transfused pretransplantation (eg, other hemoglobinopathies and bone marrow failure syndromes) are particularly at risk for iron overload and acquired hepatitis B virus and HCV infections.

Recommendations

1. LFTs (total bilirubin, alkaline phosphatase, and transaminases) should be performed every 3 to 6 months for the first year and then at least yearly thereafter. More frequent assessments may be needed based on an individual patient's medical status (eg, patients with GVHD) and particularly in allogeneic transplantation survivors.
2. Patients with hepatitis B and HCV should have viral load monitored by polymerase chain reaction, and consultation with liver and infectious disease specialists for antiviral therapy is advised. Liver specialists may recommend a liver biopsy in patients with chronic HCV infection to determine the extent of cirrhosis. This is particularly important in patients 8 to 10 years posttransplantation.
3. Serum ferritin should be measured at 1 year posttransplantation in patients who received RBC infusions pre- or posttransplantation. Subsequent monitoring with serum ferritin should be considered among patients with elevated levels, especially in the presence of abnormal LFTs, continued RBC transfusions, or HCV infection. Additional diagnostic testing (eg, liver biopsy, MRI or SQUID) may be indicated if therapy is contemplated for suspected iron overload.

RENAL AND GENITOURINARY COMPLICATIONS

Renal dysfunction among HCT survivors can be caused by a number of exposures in the pre-, peri-, and posttransplantation period. The incidence of chronic kidney disease (CKD), defined as sustained decrease in glomerular filtration rate below 60 mL/min/1.73 m², has been reported to range from 5% to 65% [41,42]. CKD usually becomes apparent 6 to 12 months after transplantation, although it can occur earlier as well as much later posttransplantation. Renal dysfunction may present as thrombotic microangiopathy, glomerulonephritis, or nephrotic syndrome, and radiation nephritis may occur after exposure to TBI. The majority of patients have an idiopathic form of CKD, which is not associated with thrombotic microangiopathy or nephrotic syndrome and has a multifactorial etiology.

Risk factors for CKD in long-term survivors of HCT include older age at HCT, diagnosis (eg, myeloma) and pretransplantation renal function and therapy exposures (eg, platinum compounds), acute GVHD and cGVHD, use of TBI in conditioning regimen, exposure to medications to prevent or treat GVHD (eg, calcineurin inhibitors), and certain antimicrobials (eg, acyclovir, amphotericin B, aminoglycoside antibiotics) [42,43]. Antibiotics and antifungal

agents cause tubular rather than glomerular damage. Calcineurin inhibitors can cause glomerular thrombosis and tubular injury. A long-term syndrome of calcineurin inhibitor-associated renal injury can affect both renal arterioles and tubules and can be accompanied by interstitial fibrosis. CMV infection has also been associated with glomerular injury, and the use of foscarnet for CMV infection can further induce tubulointerstitial nephritis and irreversible damage because of crystallization within the renal tubules. Radiation exposure (eg, TBI) can lead to degeneration and sclerosis of arterioles and secondary destruction of glomeruli and tubules.

Patients with substantial hemorrhagic cystitis in the early posttransplantation period experience a greater risk of later bladder wall scarring and contraction. Evaluation and treatment of polyoma or adenoviruses may be warranted in some patients with hemorrhagic cystitis, especially if they have received an extended duration of immunosuppressive therapy. Patients receiving immunosuppressive therapy for cGVHD, particularly women with GVHD of the vulva and vagina are at risk of recurrent urinary tract infections.

Recommendations regarding complications of the genital and reproductive organs are also addressed in the Endocrine Complications and Mucocutaneous Complications sections.

Recommendations

1. Blood pressure should be checked at every clinic visit, and hypertension should be investigated and managed appropriately in all HCT recipients (see section on General Screening and Preventive Health).
2. Renal function should be evaluated at 6 months, 1 year, and at least yearly thereafter for all HCT recipients. Screening should include assessment of BUN, creatinine, and urine protein. Further workup (eg, renal ultrasound, renal biopsy), as clinically indicated should be pursued in patients with late-onset acute renal failure or CKD posttransplantation. More frequent assessments may be needed based on an individual patient's medical status (eg, ongoing therapy with calcineurin inhibitors).
3. In patients with progressive CKD, avoid nephrotoxins and consider early referral to a nephrologist for evaluation and treatment.

COMPLICATIONS OF MUSCLE AND CONNECTIVE TISSUE

Major late complications affecting muscle and connective tissue after HCT include steroid-induced myopathy, fasciitis/scleroderma, and polymyositis.

One case-matched control study reported that 35% of 10-year survivors after HSCT still complain of musculoskeletal stiffness, cramps, weakness, and joint swelling, and the incidence of musculoskeletal problems was significantly higher than controls [44]. Possible causes of these problems may include sedentary lifestyle combined with muscle loss, myopathy, or fibromyalgia related to steroid treatment, or scleroderma/fasciitis related to cGVHD.

Myopathy after HCT is one of the most frequent complications of long-term steroid therapy for cGVHD. It is associated with moderate to severe functional impairment and may also be associated with an increased risk of mortality. Proximal lower extremity muscles are commonly involved, with the quadriceps muscle being most severely affected. The myopathy progresses insidiously in most cases. Clinical observation of a patient changing position from supine to sitting or sitting to standing may reveal early myopathy. The use of a questionnaire such as the Human Activity Profile may lead to its early detection [45]. Posttransplantation fatigue contributes to inactivity, which exacerbates muscle atrophy. Therefore, it is also important to encourage progressively increasing physical activity to stop this vicious cycle.

Myositis or polymyositis is a distinctive feature of cGVHD as defined by National Institutes of Health consensus criteria [29]. Although the incidence of myositis in patients with cGVHD is much higher than in the general population, it is a rare complication after HCT. Chronic GVHD-associated polymyositis or myopathy usually occurs 2 to 5 years after HCT, and the common presenting symptoms are moderate to severe proximal muscle weakness and/or myalgia. Lower extremities are more commonly involved. This syndrome may be hard to distinguish from steroid-induced myopathy. The majority of patients have elevated serum creatinine kinase (CK) levels, a myopathic pattern on electromyography, a largely perifascicular lymphocytic infiltration on muscle biopsy, and a very favorable response to immunosuppressive therapy [46]. It is often a challenge to differentiate the muscular weakness of cGVHD-associated myositis or myopathy from that of steroid myopathy/peripheral neuropathy, as a few patients with cGVHD-associated myopathy have a normal CK level and lack lymphocytic infiltration in the muscle biopsy.

Sclerosis can affect the skin and subcutaneous tissues including fasciae, joints, and the musculoskeletal system with varying degrees of severity and is a diagnostic feature of cGVHD. Early involvement of fasciae and tendons is associated with edema and an eosinophilic infiltrate, with later progression to fibrosis and joint contractures, most commonly in fingers, wrists, shoulders, elbows, and ankles. Inflammation of the synovium may produce joint effusion. As sclerosis

progresses insidiously, early detection is often difficult. Aggressive and prolonged immunosuppressive therapy is necessary to prevent progression of contractures, but it is usually ineffective at reversing established contractures. Early intervention and rehabilitation become essential to restore range of motion and strength. Stretching exercises and myofascial massage are important to help improve the range of motion of affected joints and to restore functions of daily living [18]. Regular survey of range of motion at all target joints by clinicians as well as patients is also essential to detect early and potentially reversible limitation of movement.

The presence of a variety of autoantibodies such as antismooth muscle, antinuclear, and antimitochondrial antibodies after HCT has been observed, but in most cases, they are not associated with any clinical symptoms. However, in rare cases, donor-derived anti-acetylcholine receptor antibodies may be present with clinical manifestations of myasthenia gravis [47]. Adoptive transfer of abnormal lymphocyte clones has been suggested as a possible mechanism, but immune dysregulation associated with concomitant cGVHD might be a contributing factor.

Recommendations

1. All HCT recipients should follow general population age-specific guidelines for physical activity (See section on General Screening and Preventive Health).
2. For patients on corticosteroids, frequent clinical evaluation is recommended for steroid-induced myopathy by manual muscle tests or by assessing patients' ability to go from a sitting to a standing position.
3. Patients with muscle weakness, myalgias, or arthralgias should be evaluated for possible cGVHD or steroid-associated myositis and other muscular disorders (eg, myasthenia gravis).
4. Among patients with cGVHD, joint range of motion should be evaluated to detect sclerotic changes. Patients should also be instructed to perform self-assessment of range of motion.
5. Where prolonged corticosteroid exposure is anticipated or when fasciitis or scleroderma develops, a physical therapy consultation should be considered to establish baseline function and provide range of motion and muscle strengthening exercises to minimize loss of function.

SKELETAL COMPLICATIONS

Bone density loss is a well-recognized complication of HCT. There is a wide variation in the reported incidence of this complication; some studies have reported incidence rates as high as 25% for osteoporosis

and 50% for osteopenia [48-51]. Rapid loss of bone usually takes place within 6 to 12 months after transplantation. Certain patients are more susceptible to bone loss including elderly, women, patients with low body weight (body mass index <20 to 25 kg/m²), patients who are physically inactive, and patients who receive extended corticosteroid therapy for their underlying disease before transplantation or for GVHD after transplantation. Some experts consider prolonged corticosteroid exposure as use of ≥ 5 mg prednisone equivalent daily for >3 months [52]. Providers should also consider corticosteroid exposure pretransplantation when determining risk for bone loss (eg, as part of treatment regimens for lymphoma and acute lymphoblastic leukemia). The use of calcineurin inhibitors and other immunosuppressive therapy may increase the risk for this complication.

Studies suggest that both the total cumulative dose and the duration of corticosteroid therapy are important factors for the development of osteopenia [48]. Other possible contributing factors include hypogonadism, secondary hyperparathyroidism because of the decrease in serum levels of calcium and vitamin D, and direct toxicity from conditioning to bone cells and bone marrow stromal cells. Standard preventive measures include adequate physical activity in the posttransplantation period, use of supplemental calcium and vitamin D, and consideration of estrogen replacement therapy in deficient women.

Dual photon densitometry is currently the best tool to assess the degree of bone loss. Osteopenia and osteoporosis are differentiated by the degree of reduction in bone mass and can be quantified by T and Z scores by dual photon densitometry. Normal values of bone density have not been well established in children, although it is clear that the loss of bone density and increased risk of fracture is a significant issue in children after HCT. The femur neck and lumbar spine are the two most frequently measured sites by bone densitometry. Studies have shown differential effects in the extent and length of post-HCT bone density loss. Bone loss is more severe, persistent, and resistant to therapy in cortical bones such as the femur neck than in trabecular bones such as the spine.

Treatment choices for patients with established osteopenia and osteoporosis include active exercise, calcium and vitamin D supplementation, use of estrogen replacement in women, and minimizing the total exposure and duration of steroid and other immunosuppressive therapy, if possible [48]. Bisphosphonate therapy should be considered for treatment of patients with established osteopenia and osteoporosis, patients with evidence of progressive bone density loss, and patients at high risk for bone loss (eg, patients with GVHD on extended steroid therapy). The optimal schedule and duration of bisphosphonate therapy in HCT is not well established. Bisphosphonate therapy

has also been used in addition to calcium and vitamin D supplementation as a preventive measure for patients at high risk for osteopenia and osteoporosis, although the data for this intervention are less clear. Osteonecrosis of the jaw has been reported in patients receiving bisphosphonates for osteoporosis, especially among those undergoing oral procedures while on these agents [53]. If appropriate, dental evaluation should be performed before starting bisphosphonates in order to detect and correct any dental problems. Long-term use of bisphosphonates may be associated with subtrochanteric fractures of the femur; extended duration of therapy with these agents should be carefully considered until more information about this association becomes available [54].

Avascular necrosis (AVN) has been described in 4% to 19% of HCT survivors. In addition to the risk factors for post-HCT bone loss, inflammatory microvascular changes related to GVHD or other factors may contribute to this complication [55,56]. TBI has been associated with a higher incidence of AVN in some reports. Joint pain or discomfort is usually the first manifestation of AVN, and standard radiographic evaluation may not detect abnormalities until late in the disease course. Joint symptoms in patients at risk should prompt MRI for early detection. Although the hip is the most frequently affected joint (over 80% of cases; bilateral in more than 60%), other joints can be affected, including the knees, wrists, and ankles. Symptomatic relief of pain and orthopedic measures to decrease pressure on the joint can be helpful. Most adult patients with advanced AVN will require surgical intervention. Orthopedic procedures including core decompression in early cases and joint replacement provide a satisfactory outcome in most patients. However, long-term follow-up of these procedures is needed in younger patients with a long life expectancy.

Recommendations

1. A screening dual photon densitometry should be performed at 1 year after transplantation in adult women, all allogeneic HCT recipients, and patients who are at high risk for bone loss after transplantation (eg, prolonged treatment with corticosteroids or calcineurin inhibitors). Repeat densitometry should be performed in those with recognized defects, ongoing risk factors, or to follow-up response to therapy. Physicians should evaluate gonadal and other related endocrine abnormalities in patients with decline in bone density.
2. Patients should be counseled about preventive measures for bone loss and fractures such as physical exercise, fall prevention, and vitamin D and calcium supplementation. Hormone replacement therapy should be discussed with women who have estrogen

deficiency. Some experts recommend the use of bisphosphonates for patients at high risk for bone loss.

3. Screening for AVN is not recommended; however, clinicians should maintain a high level of suspicion for patients with exposure to irradiation or prolonged corticosteroids and evaluate patients with joint symptoms promptly.

CENTRAL AND PERIPHERAL NERVOUS SYSTEM COMPLICATIONS

Neurologic complications after HCT may affect the central and peripheral nervous system and are mostly secondary to infections, drug-related toxicity, and metabolic encephalopathy. The effect on cognitive function and level of alertness can be subclinical with white matter changes detected up to a year later. The reported complication rate is higher in allogeneic, especially alternative donor HCT, compared with autologous HCT recipients [57,58].

Complications include central nervous system infections in immunocompromised recipients and vascular complications such as stroke and calcineurin inhibitor-induced neurotoxicity. Leukoencephalopathy may occur as sequela of intrathecal chemotherapy and cranial irradiation. Patients who have received TBI or cranial irradiation are at increased risk of secondary solid tumors of the brain on long-term follow-up. Children exposed to TBI are also at risk for developmental delays. There is growing evidence of a GVHD effect on the central nervous system. A cerebral angitis-like syndrome has been described with cerebral ischemic lesions and leukoencephalopathy secondary to GVHD. Guillain-Barre – like syndrome with peripheral neuropathy and chronic demyelinating polyneuropathy related to GVHD has been reported [47,59,60]. Peripheral neuropathy after HCT may be related to chemotherapy exposure.

Neuropsychologic deficits have been described in nearly 20% of recipients and cognitive deficits in approximately 10% of HCT recipients. Patients with a history of central nervous system disease (eg, adenosine deaminase deficiency-associated severe combined immunodeficiency) and children treated with cranial radiation alone or in combination with chemotherapy are at higher risk. Cognitive changes may be subtle and difficult to detect, making it imperative for the clinician to be vigilant even in patients who do not have any specific complaints [59,61]. Neurocognitive function generally improves over time, but long-term deficits can remain in more than 40% of survivors [62].

Recommendations

1. All HCT recipients should undergo clinical assessment for symptoms or signs of neurologic

dysfunction at 1 year after HCT and at least yearly thereafter. Earlier and more frequent evaluations may be considered in high-risk patients (eg, allogeneic HCT recipients, patients receiving prolonged immune suppression with calcineurin inhibitors, patients receiving TBI, cranial radiation, or intrathecal chemotherapy, and patients with cGVHD).

2. Evaluation for cognitive developmental milestones should be performed at least annually in pediatric patients. Adult patients should be queried annually for changes in cognitive function, which may be subtle.
3. Further evaluation (eg, MRI, nerve conduction studies, electromyography, neuropsychiatry testing) may be warranted in recipients with symptoms or signs of neurologic or cognitive dysfunction.

ENDOCRINE COMPLICATIONS

Chemotherapy, radiation therapy, and HCT can all result in impairment of endocrine function. The most significant endocrine complications are associated with exposure to radiation and chemotherapeutic agents (eg, busulfan), cGVHD, and prolonged corticosteroid exposure [63].

Subclinical, compensated hypothyroidism, with elevated TSH and normal serum-free T4 levels, occurs in 7% to 15% of patients in the first year after transplantation. The reported incidence of frank hypothyroidism is variable depending on risk factors in the population studied. Single-dose ablative TBI is associated with a 50% incidence of overt hypothyroidism, whereas fractionated TBI is associated with an incidence of about 15%. The incidence reported after busulfan and cyclophosphamide conditioning is 11%. Treatments given before transplantation likely also contribute to the risk of thyroid abnormalities. The median time to diagnosis of hypothyroidism is nearly 4 years after HCT or TBI exposure. When TSH is elevated with normal T4 levels, assessment should be repeated in 2 months, or therapy should be initiated at the discretion of the treating physician. Patients who start thyroid hormone replacement should be reassessed at about 6 weeks after initiation of therapy. Further individual dose adjustment should be based on periodic thyroid assessment, most often recommended at 6-month intervals. Autoimmune thyroiditis may also occur following radiation. Radiation to the neck and TBI has been associated with dose-related increases in risk of thyroid malignancy, often with long latent periods [64].

Gonadal dysfunction is highly prevalent in HCT recipients, with rates as high as 92% for males and 99% for females. The degree of dysfunction depends

on age, gender, pretransplantation therapy, and conditioning regimen [65]. Although the risk of gonadal failure is high in all individuals, women generally experience higher rates of failure than do men.

Women are at high risk of hypergonadotropic hypogonadism after HCT [66]. Hypogonadism is nearly universal after high-dose irradiation or busulfan. The risk is lower with cyclophosphamide alone. In general, ovarian endocrine failure is irreversible in adult women, but younger women, particularly prepubescent girls, have a better opportunity for recovery of gonadal function.

Fractionation of radiation reduces the risk compared with unfractionated radiation. Prepubertal girls should be monitored closely for onset of puberty and, if puberty is not experienced by age 12 to 13, be referred for full endocrinology evaluation and consideration of hormone supplementation. Adult women should be evaluated by a gynecologist and may require hormone replacement therapy to maintain libido, sexual function, and bone density. Libido is often decreased and only partially corrected by hormone replacement therapy in women. Vaginal GVHD may result in strictures and synechiae. Supplemental vaginal lubrication is available and should be discussed by the treating physician.

Most men have normal testosterone levels after transplantation, although germ cell damage (infertility) is a near-universal finding in men exposed to high doses of radiation or chemotherapy. Most reports suggest that prepubertal boys experience normal puberty and demonstrate normal testosterone levels following HCT [66]. Testing and consideration of hormone replacement therapy for men is recommended based on symptoms. Failure to progress through puberty in a timely fashion should prompt referral for a full endocrinology evaluation.

Transplantation recipients have a low incidence of primary adrenal failure after HCT. Chronic therapy with corticosteroids for GVHD will suppress the pituitary-adrenal axis, but function usually recovers gradually once exogenous corticosteroid exposure ends. Greater length and intensity of exposure is generally associated with longer persistence of adrenal suppression. Patients with prolonged exposure to corticosteroids after HCT should have adrenal axis testing when withdrawing corticosteroids, particularly if symptoms of adrenal insufficiency develop. Clinicians should maintain awareness of possible hypoadrenalism in patients receiving long-term corticosteroids who develop acute illness and consider "stress-dose" corticosteroids.

Growth in children may be adversely affected by HCT, depending on their pretransplantation therapy and conditioning regimen [65,66]. A large body of data suggests that radiation is associated with growth defects in children who receive HCT.

Cranial radiation, in particular, increases the risk of diminished growth in children. Some reports suggest that chemotherapy alone may cause growth deficiencies. Growth is a complicated process and may be adversely affected by many additional factors, including general illness, nutritional deficits, hormonal deficiencies, long-term corticosteroids, and GVHD. The risk of impaired growth is greatest in the youngest children. Children should be closely monitored for appropriate growth velocity after HCT. A pediatric endocrinologist should evaluate children who do not achieve adequate growth, and assessment of growth hormone levels should be considered. Growth hormone deficiency following TBI has been shown in some studies but not in others. Because growth failure is likely to be multifactorial, consideration must be given to causes other than inadequate growth hormone. The benefits of growth hormone supplementation are unclear. However, in children with demonstrated deficiency, supplementation is commonly prescribed.

Recommendations

1. Thyroid function tests (TSH, T3, and free T4) should be performed at 1 year and yearly thereafter in all transplantation recipients and additionally if relevant symptoms develop.
2. Clinical and endocrinologic gonadal assessment at 1 year after HCT is recommended for all women who were postpubertal at the time of transplantation. Frequency of subsequent assessments should be guided by clinical need (eg, menopausal status). Women should have annual gynecologic evaluation as part of general health screening, at which time, hormone replacement therapy should be addressed for those who are postmenopausal.
3. Gonadal function in men, particularly FSH, LH, and testosterone, should be assessed if symptoms warrant (lack of libido or erectile dysfunction). Consider referral to an endocrinologist for men who may need testosterone replacement therapy.
4. Clinical and endocrinologic gonadal assessment of prepubertal boys and girls should be initiated 6 to 12 months after transplantation, with further follow-up schedule determined in consultation with an endocrinologist.
5. Patients withdrawing from prolonged corticosteroid usage should have slow terminal tapering of corticosteroids; stress doses of corticosteroids may be warranted during acute illness in patients who have been on chronic corticosteroids in the past.
6. Growth velocity should be monitored every year in all children, with assessment of thyroid function and growth hormone if growth velocity is abnormal.

MUCOCUTANEOUS COMPLICATIONS

Late complications involving skin and appendages are frequent after HCT [67]. Nearly 70% of patients with cGVHD experience skin involvement. Early changes of lichen planus-like or papulosquamous lesions may progress to sclerosis or poikiloderma and can be associated with skin ulcers and subsequent infections. Alopecia, thinning of scalp hair, nail dystrophy, sweat impairment, and skin dyspigmentation are common complications after cGVHD.

HCT survivors, especially recipients of allogeneic HCT, are at risk for developing secondary cancers of the skin [24]. Patients should be counseled about early detection and prevention of skin cancers including avoiding excessive sun exposure, using adequate skin protection and periodic self-examination of the skin with prompt referral to a dermatologist for further evaluation and treatment of suspicious skin lesions.

Severe genital GVHD may develop in approximately 12% of women with or without associated systemic GVHD [68,69]. Patients may present with excoriated or ulcerated mucosa, fissures, narrowing of introitus, or vaginal scarring and obliteration that may lead to hematocolpos. Initial symptoms may be mild and nonspecific such as dryness, dyspareunia, or postcoital bleeding, and if not recognized, they may lead to important sexual dysfunction. Careful questioning and examination should be performed, as patients without sexual activity may not detect these abnormalities, and sexually active patients may not disclose relevant symptoms. Biopsy may be needed to establish the diagnosis. Care should be taken when reducing systemic immunosuppression, as reactivation of genital GVHD may occur. Vaginal strictures may limit the performance of routine Papanicolaou smears as well as sexual intercourse. Treatment of vaginal GVHD includes topical steroids, topical cyclosporine, and vaginal dilators. Surgical intervention can be used to treat severe cases. In contrast to cGVHD, patients with hypoestrogenism because of premature menopause may present with thin and pale vulvar mucosa that responds well to lubricants and topical estrogens. However, patients may have changes because of GVHD and hypoestrogenism concurrently. Genital involvement with GVHD is less common in men and may result in phimosis.

Recommendations

1. Patients should perform routine self-examination of the skin and avoid excessive exposure of sunlight without adequate protection.
2. All female recipients of allogeneic HCT should have clinical screening for symptoms of genital GVHD. Women who have established cGVHD

should have a gynecologic exam to screen for genital involvement.

3. Patients should be counseled about self-examination of the vaginal area, general hygiene measures, and early recognition of local symptoms. Application of topical vaginal immunosuppressive agents, such as ultrahigh-potency corticosteroids or calcineurin inhibitors, prescription of systemic hormonal replacement therapy if indicated, and the use of vaginal dilators should be initiated early in the course of the disease.

SECONDARY CANCERS

Second malignancies after HCT are a devastating late complication. Patients receiving allogeneic HCT have a two to three fold increased risk of developing solid tumors, compared with an age-, gender-, and region-adjusted population [59]. Nearly all cancer types are described after allogeneic and autologous transplantation, including oral cancers, as mentioned previously. Risk factors include radiation therapy, length, and intensity of immunosuppression and cGVHD [26]. However, a recent long-term follow-up analysis of patients who underwent transplantation after myeloablative doses of busulfan and cyclophosphamide found similar increased risk [25]. Risk increases with time after transplantation, particularly for radiation-related malignancies. Recent analyses suggest that risk of radiation-related (sarcoma, breast, and thyroid cancers) and nonradiation-related (squamous cell carcinoma linked to cGVHD) solid tumors continues to increase beyond 10 years posttransplantation [24,26]. Children who have received cranial irradiation are at risk for developing brain tumors. HCT recipients with Fanconi's anemia are also at risk for developing oropharyngeal cancers. Providers can consider vaccination against the human papilloma virus according to country-specific general population recommendations [10]. All patients should at least receive country-specific general population recommendations for screening for cancers. Screening for breast cancer is recommended at an earlier age (25 years or 8 years after radiation, whichever occurs later) but no later than age 40 among recipients of TBI or chest irradiation. Early referral to a dermatologist should be considered in patients with skin lesions suspicious for cancer.

Risk of secondary leukemia or myelodysplasia after autologous HCT is also higher than anticipated, with an overall incidence of about 4% at 7 years after transplantation, with a median onset of 2.5 years (range, 3 months to 7 years) posttransplantation. Risk appears to be increased for patients receiving prior alkylator therapy, prolonged administration of conventional chemotherapy, and higher doses of pretransplantation irradiation [70].

Posttransplantation lymphoproliferative disorders (PTLD) are a rare complication of allogeneic HCT associated with greater donor-recipient HLA disparity, T cell depletion, and GVHD [71]. Overall incidence is 1% at 10 years after HCT. Although these usually occur early (within 6 months of transplantation), PTLD is reported as late as 8 years after HCT. The majority of PTLD are associated with Epstein-Barr virus infection. Quantitative polymerase chain reaction detection of Epstein-Barr virus reactivation allows prompt initiation of anti-CD20 monoclonal antibody therapy before development of frank PTLD [59].

Recommendations

1. Exposure to radiation and photosensitizing effects of many commonly used transplantation-related medications increases the risk of skin cancers among HCT recipients. All HCT recipients should be encouraged to reduce UV skin exposure through use of high SPF sunscreens or skin coverage.
2. All patients should be advised of the risks of secondary malignancies annually and encouraged to routinely perform recommended screening self-examination such as genital/testicular and skin examination. Women should discuss breast self-examination with their physicians. All patients should be encouraged to avoid high-risk behaviors as recommended under the General Health and Preventive Screening section, including avoidance of tobacco, passive tobacco exposure, or excessive unprotected skin UV exposure.
3. Screening clinical assessment should be performed yearly and should include symptom review for secondary malignancies. Clinical examination and screening for secondary malignancies should follow the recommendations outlined under the General Health and Preventive Screening section. In women with radiation exposure (eg, TBI or radiation to the chest region), initiation of screening mammography should occur at age 25 or 8 years after radiation, whichever occurs later, but no later than age 40 years. Particular attention to oral malignancies should be paid to patients with previous severe cGVHD of the oral and pharyngeal mucosa.

PSYCHOSOCIAL ADJUSTMENT AND SEXUAL COMPLICATIONS

Depressive symptoms and psychologic distress are frequently observed in HCT survivors. Fatigue, anger, insomnia, and problems with marital relationships may also be seen. Pediatric patients may experience altered behavior patterns, changes in social habits, and changes in academic/school behavior. At the transition from acute convalescence to long-term follow-up,

psychological distress may increase rather than abate as the patient and his/her family must cope with changes in roles, employment situations, and financial difficulties. Spouses and other caregivers may also exhibit high levels of depression and psychological distress. They often report loneliness and low levels of perceived social support. Children may suffer from separation from one or both parents and the consequences of stress and upheaval in the family. At a minimum, screening for depression is recommended every 6 to 12 months after transplantation as per the general health maintenance section (information to follow). Specific tools for screening for psychosocial difficulties after HCT are also available and could be used with a similar frequency to depression screening. Sexual dysfunction occurs in a significant number of survivors and may be multifactorial in origin, from depression to gonadal hormonal deficiency.

Recommendations

1. A high level of vigilance for psychological symptoms should be maintained. Clinical assessment is recommended throughout the recovery period, at 6 months, at 1 year, and at least yearly thereafter, with mental health professional assessment recommended for those with recognized deficits.
2. Inquiry as to the level of spousal/caregiver psychological adjustment and family functioning should be performed at regular intervals.
3. In adults, sexual function should be queried at 6 months, at 1 year, and yearly thereafter (see also the section on Mucocutaneous Complications).

FERTILITY

Male and female HCT survivors are at risk for infertility secondary to pretransplantation and transplantation-related treatment exposures [72,73]. Among transplantation survivors of the child-bearing age group, loss of fertility can be associated with psychological consequences that can affect quality of life. Conditioning regimens with TBI or busulfan plus cyclophosphamide can cause gonadal failure, although risk may be lower with regimens that include cyclophosphamide only. Older age at transplantation and cGVHD are associated with a low likelihood of gonadal recovery. Nonassisted natural pregnancies following gonadal recovery in women or in partners of male transplantation recipients have been reported, but the estimated incidence is <15%.

The outcome of pregnancy after transplantation is generally good, although women are at increased risk of fetal and maternal complications, and posttransplantation pregnancy should be considered a high-risk pregnancy [73]. The incidence of congenital

anomalies is not higher than in the normal population, and the rate of miscarriage is not increased. Women exposed to TBI have a higher than normal incidence of preterm deliveries and low or very low birth weight infants. Irradiation may result in uterine vessel damage and reduce uterine volume.

A general recommendation is to delay spontaneous or assisted pregnancies for at least 2 years after HCT, because this is the period of highest risk of relapse after transplantation. Contraception counseling in survivors after HCT with gonadal recovery is recommended, and contraception is advisable if fertile or if fertility status is not known and pregnancy is not desired. Even if the patient is infertile, barrier contraception is recommended with new partners to prevent sexually transmitted diseases.

Women with gonadal recovery should also be advised about the risks of premature menopause.

Recommendations

1. Consider referral to appropriate specialists for patients who are contemplating a pregnancy or are having difficulty conceiving.
2. Although infertility is common, patients should be counselled regarding birth control posttransplantation.

GENERAL SCREENING AND PREVENTIVE HEALTH

In addition to transplantation-specific risk factors mentioned previously, HCT survivors face general risks found in the population that has not undergone transplantation. In general, transplantation survivors should be under the care of physicians comfortable with providing care for general health and hematology-oncology specific issues. Summarized below are screening and lifestyle recommendations for the general adult population that are also relevant for HCT survivors. Further details about screening recommendations for adults and children can be found at: <http://www.uspreventiveservicestaskforce.org> [74,75].

Recommended Screening for All Patients

1. Hypertension: Blood pressure should be checked at least every 2 years. In children, hypertension is defined as readings greater than the 95th percentile for age, sex, and height. Treatment is indicated for readings of greater than 140/90 in adults on two separate visits at least 1 week apart, unless hypertension is mild or can be attributed to a temporary condition or medication (eg, cyclosporine). Nonpharmacologic treatments may also be tried for mild hypertension and include moderate dietary sodium

- restriction, weight reduction in the obese, avoidance of excess alcohol intake, and regular aerobic exercise.
2. Hypercholesterolemia: Cholesterol and HDL levels should be checked every 5 years starting at age 35 for men and 45 for women. Screening should start at age 20 for anyone who smokes, has diabetes, hypertension, obesity (body mass index ≥ 30 kg/m²), or a family history of heart disease before age 50 for male relatives or before age 60 for female relatives. Fasting is not required for accurate measurement of cholesterol and HDL, but it is required for LDL and triglycerides. As a rough guideline, total cholesterol levels >200 mg/dL (>5.0 mmol/L) or HDL levels <40 mg/dL (<1 mmol/L) should be followed up by a full fasting lipid panel. Treatment goals are based on overall risk of heart disease (eg, $>10\%$ chance of coronary heart disease in 10 years). Overall risk assessment will include the following risk factors: age, sex, diabetes, clinical atherosclerotic disease, hypertension, family history, low HDL (<40 mg/dL or 1.0 mmol/L), and smoking. An online calculator is available at <http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm>.
 3. Colorectal cancer: Screening should start at age 50 in the absence of a family history (first-degree relative diagnosed with colorectal cancer before age 60). The interval of testing depends on the type of testing procedure and the prior screening results. There are several screening approaches including annual fecal occult blood testing (three cards at home), sigmoidoscopy every 5 years with fecal occult testing every 3 years, or colonoscopy every 10 years. Virtual computerized tomography is a new method, currently under investigation. The No. 1 approach alone or in combination has proven superior; however, a single digital rectal exam with occult blood testing is not recommended.
 4. Diabetes: Screening for type 2 diabetes is indicated for people every 3 years after age 45 or in those with sustained higher blood pressure ($>135/80$) because blood pressure targets are lower for diabetics. A fasting plasma glucose >126 mg/dL (>7 mmol/L), confirmed by testing on another day, is diagnostic for diabetes.
 5. Depression: Asking two simple questions about mood and anhedonia (“Over the past 2 weeks, have you felt down, depressed, or hopeless?” and “Over the past 2 weeks, have you felt little interest or pleasure in doing things?”) is probably as effective as longer screening tools. Frequency of screening is not stated, but it is reasonable to screen every 6 to 12 months posttransplantation or as clinically indicated. Affirmative answers to the questions above should trigger in-depth evaluation for depression to determine the need for pharmacological or psychotherapeutic treatments.

6. Sexually transmitted diseases: Chlamydia screening is recommended for women under the age of 25 who are sexually active. Screening and appropriate treatment decrease the incidence of pelvic inflammatory disease and pregnancy-related complications, although most women will be infertile after myeloablative transplantation. Male and female survivors should be reminded that protection against sexually transmitted disease is important even when pregnancy is unlikely or impossible.

SEX-SPECIFIC RECOMMENDATIONS

Recommended Screening for Men

1. Prostate cancer: There is no consensus about the use of prostate-specific antigen or digital rectal examination for prostate cancer screening.

Recommended Screening for Women

1. Breast cancer: Screening with mammograms should start at age 40 and occur every 1 to 2 years. Breast self-exam is not recommended. In women exposed to >800 cGy radiation, screening should start at age 25 or 8 years after radiation exposure, whichever is later but no later than age 40, based on the data from Hodgkin lymphoma survivors.
2. Cervical cancer: Screening with pap smears should be performed every 1 to 3 years in women older than 21 or within 3 years of initial sexual activity, whichever occurs earlier.
3. Osteoporosis: Screening with a bone density test should start at age 65 for women in the general population or if the individual’s fracture risk is equivalent to a 65-year-old woman (9.3% risk at 10 years) [76]. An online calculator is available to determine the 10-year risk of fracture (www.shef.ac.uk/FRAX/). Also see the section on Skeletal Complications for additional recommendations for HCT recipients.

Healthy Lifestyle Recommendations for All Patients

1. Eat a healthy diet with a wide variety of foods.
2. Don’t smoke (passive or active exposure), chew tobacco, or use illegal drugs.
3. Use alcohol in moderation, generally $<$ two drinks per day.
4. Maintain a healthy weight.
5. Avoid excessive sun exposure and wear sunscreen protection for anticipated periods of long exposure.
6. Follow general population age-specific guidelines for physical activity (www.health.gov/paguidelines) [77]. Adults (aged 18-64) should do 2 hours and 30

minutes a week of moderate-intensity, or 1 hour and 15 minutes a week of vigorous-intensity aerobic physical activity or an equivalent combination of moderate- and vigorous-intensity aerobic physical activity. Aerobic activity should be performed in episodes of at least 10 minutes. Adults should also do muscle strengthening activities that involve all major muscle groups performed on 2 or more days per week.

IMPLEMENTATION OF GUIDELINES IN RESOURCE-LIMITED COUNTRIES

Although the Working Group has provided recommendations that should be applicable to all HCT recipients, they recognized that resource constraints may limit their implementation, especially in certain geographic regions and developing countries. Some examples of such challenges include the availability of specialists with expertise and experience in managing posttransplantation complications and availability of tests and procedures. Furthermore, issues related to healthcare access (eg, distance to transplantation center or healthcare facility with adequate expertise and resources) may restrict the ability of some patients to obtain screening and preventive care. In circumstances where resource limitations do not allow for comprehensive evaluation and follow-up, healthcare providers should use their best clinical judgment in determining appropriate preventive care for HCT survivors based on their individual exposures and risk factors for long-term complications.

LONG-TERM FOLLOW-UP OF HCT RECIPIENTS

To facilitate the transition of HCT recipients from one phase of posttransplantation care to another, transplantation providers should provide HCT recipients with a survivorship care plan that includes a treatment summary and a follow-up care plan. This document can serve as an instrument for reminding providers about appropriate surveillance for late complications based on an individual patient's risk factors and exposures. Because survivors can be at risk for late relapse, the care plan should also include appropriate follow-up for the disease for which HCT was performed. Survivorship care plan instruments that are specific to HCT recipients are lacking. Until they are routinely available, providers can consider instruments that have been developed for cancer survivors in general (eg, LIVESTRONG Care Plan [www.livestrong-careplan.org], Passport for Care® [www.txch.org/passportforcare]). In addition, providers can consider incorporating the patient version of these guidelines

(available at www.BeTheMatch.org/Patient) into a survivorship care plan document for HCT recipients.

Long-term survivors of HCT may not receive care at their transplantation center. Because of patient or center preference, absence of immediate transplantation-related complications, or distance from the transplantation center, transplantation recipients may transition their care back to their hematologist-oncologists, primary care physicians, or other healthcare providers. With an increasing number of transplantation survivors, it is likely that nontransplantation healthcare providers will play a greater role in survivorship care and may need to be aware of the unique exposures, risk factors, and medical issues these patients face. The working group recognized that the models and primary site for long-term follow-up will vary by country and available resources. On occasion, adherence to particular recommendations may be inconsistent with national or regional guidelines, the availability of specific procedures or medications, or local epidemiologic conditions. Individual clinicians should practice best clinical judgment in implementing these guidelines and when caring for an individual patient, should consider age, gender, coexisting comorbidities, cancer, and transplantation-related exposures and immediate side effects in determining patient risks for specific long-term complications. Prevention, screening and management of late complications of transplantation may require a multidisciplinary approach, with involvement of the transplantation center, oncologists, subspecialists, primary care physicians, and other healthcare providers, as necessary.

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SUPPLEMENTARY DATA

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