How I treat late effects in adults after allogeneic stem cell transplantation

1 Bipin N Savani, 2 Michelle L Griffith, 2 Shubhada Jagasia, and 3 Stephanie J. Lee

1 Long-Term Follow-up Transplant Clinic (LTTC), Hematology and Stem Cell Transplantation Section, Division of Hematology/Oncology, Department of Medicine, Vanderbilt University Medical Center and Veterans Affairs Medical Center, Nashville, TN, USA

2 Department of Medicine, Division of Diabetes, Endocrinology, and Metabolism, Vanderbilt University School of Medicine, Nashville, TN, USA

3 Clinical Research Division, Fred Hutchinson Cancer Research Center and the Department of Medicine, University of Washington, Seattle, WA, USA

Corresponding Author:

Bipin N. Savani, MD
Long-Term Follow-up Transplant Clinic (LTTC)
Hematology and Stem Cell Transplantation Section
Vanderbilt University Medical Center and VAMC
2655 The Vanderbilt Clinic
Nashville TN-37232-5505
USA
Phone: 615-936-1803
Fax: 615-936-1812
E-mail: Bipin.Savani@Vanderbilt.Edu

Running title: Late effects after allo HCT

Key Words: late effects; survivorship; complications; allogeneic hematopoietic cell transplantation

Declaration of commercial interest: None

Word Count: abstract: 125; text: 5,252; References: 86

Funding: SJL funding provided by CA18029
Abstract

More than 25,000 allogeneic hematopoietic stem cell transplantations (allo-HCT) are expected to be performed worldwide in 2010, a number that has been increasing yearly. With broadening indications, more options for allo-HCT, and improvement in survival, by 2020 there may be up to half a million long term survivors after allo-HCT worldwide. These patients have increased risks for various late complications which can cause morbidity and mortality. Most long term survivors return to the care of their local hematologist-oncologists or primary care physicians, who may not be familiar with specialized monitoring recommendations for this patient population. The purpose of this paper is to describe practical approaches to screening for and managing these late effects, with the goal of reducing preventable morbidity and mortality associated with allo-HCT.
Introduction

Since the first 3 cases of successful allogeneic stem cell transplantation (allo-HCT) in 1968, the number of allo-HCTs performed annually has increased steadily over the past three decades. Since 2007, more allo-HCT procedures have been performed using alternative donor stem cell sources such as volunteer unrelated donors or cord blood than related donors. With less early mortality and more widespread use of HCT, the number of long-term survivors will continue to grow. Yet, among long term survivors after allo-HCT, mortality rates are 4 to 9 fold higher than observed in an age-adjusted general population for at least 30 years after HCT, yielding an estimated 30% lower life expectancy compared with someone who has not been transplanted. Among long term survivors, the most common causes of excess deaths other than recurrent malignancy are chronic graft-versus-host disease (GVHD), infections, second malignancies, respiratory diseases and cardiovascular disease.

This paper summarizes the medical late effects observed in long term allo-HCT survivors in order to frame our recommendations for evaluation and management. Given that there are no randomized trials testing diagnostic and treatment approaches for late effects within the HCT population and only limited published guidelines, we turned to general medicine studies for guidance, augmented by our personal experiences. Therefore, this article offers practical advice and outlines our personal approaches in monitoring long term survivors after allo-HCT. Management of chronic GVHD is beyond the scope of this paper and is often managed in conjunction with transplant physicians.

Second Malignancies

Following allo-HCT, survivors have an increased risk of developing new solid cancers, with the cumulative incidence ranging from 2-6% at 10 years after transplantation. A study of 28,874 allo-HCT survivors published in 2009 reported that new solid cancers developed at twice the rate expected in the general population, with the risk increasing over time, reaching 3-fold among patients followed for 15 years or more after transplantation. As the age and life expectancy of survivors continues to rise, second malignancies are expected to become an increasingly common complication. The increased incidence of second cancers may be due to the chemotherapy and radiation conditioning used for the allogeneic transplant, immunosuppression or immune dysregulation after transplantation, the chemotherapy or radiation the patient received before transplant, or possibly genetic predisposition could contribute to both the initial malignancy and secondary cancers.

Several factors are associated with increased risk, including total body irradiation (TBI), primary disease, male sex, and pre-transplantation therapy. The risk of developing a non-squamous cell cancer is highly
associated with younger age at transplant and the use of radiation in the conditioning regimen. The risk among patients irradiated at ages under 30 years is nearly 10-times that of non-irradiated patients, while the comparable radiation-related risk for older patients (age >30 years) was 1.1. Radiation is also a significant risk factor for the development of several other solid tumors, particularly cancers of the breast, thyroid, brain, central nervous system, bone and connective tissue, and melanoma, and screening is available for some of these tumors. For the majority of these sites, risks were greater among those who survived 5 or more years after initial radiotherapy, in keeping with the latent period typical for radiation related solid cancers.

Chronic GVHD and immunosuppressive therapy (IST) are associated with squamous cell cancers (SCC) of the skin and mucosa. A particularly high risk was observed in the 1- to 4-year interval after HCT, which remained elevated among long term survivors. Duration of IST and particularly prolonged exposure to azathioprine have been associated with development of SCC.

Several oncogenic types of human papillomavirus (HPV) have been implicated in the etiology of SCC of the female genital tract and head and neck and may play a role in HCT-associated SCC.

Management approach

At a minimum, we recommend adherence to the cancer screening guidelines for the general population for skin, cervical, breast, and colon cancer. Patients with a history of chronic GVHD or who have received radiation, particularly at a younger age, should have more systematic skin evaluations by health care providers and be educated to report any concerning changes. Women who have received chest or total body radiation (800 cGy or greater) should follow the guidelines established for pediatric cancer survivors of annual mammogram screening starting at age 25 or 8 years after radiation, whichever occurs later. Women, particularly those with a history of chronic GVHD, should have yearly gynecologic exams including Pap smears. In addition, patients should have clinical monitoring for other cancers known to be elevated in HCT survivors. Patients should have oral evaluations at their 6-12 monthly dental examinations to screen for head and neck cancer. Thyroid palpation should be performed annually to identify thyroid nodules that could represent thyroid cancer. If an incidental thyroid nodule is discovered on PET scan and is 18F-FDG-avid, risk of malignancy is high, 55% in a series of healthy volunteers. American Thyroid Association guidelines recommend fine needle aspiration (FNA) of nodules > 5 mm with suspicious features in patients with high-risk history (includes external beam radiation in childhood, ionizing radiation in children or adults, family history of thyroid cancer, or 18F-FDG avid nodule on PET scanning). In general, we have a low threshold to perform ultrasound-guided FNA on patients with a HCT history.
Patients should be counseled about their higher rate of second malignancies in a way that encourages compliance with screening recommendations and discourages direct sun exposure and use of carcinogenic agents such as tobacco and alcohol. Physicians should have lower thresholds to investigate new concerning signs or symptoms of malignancy in HCT survivors than for the general population. If a second malignancy is detected, then treatment plans need to consider the patient’s prior cancer and transplant exposures, for example in planning radiation therapy. Otherwise, most cancers are managed similarly to the general population. Although the reported number of cases is small, the prognosis of most second malignancies after allo-HCT does not appear to be worse than that seen in the general population after accounting for disease stage and co-morbidities. Many transplant centers also participate in studies of second cancers and would appreciate notification if their survivors develop second cancers.

**Late infections**

Immune reconstitution has a pivotal role in preventing long-term complications after allo-HCT by preventing infectious morbidity and mortality. Poor immune reconstitution may theoretically also contribute to the increased risk of malignancies after HCT.\(^{19,20,27}\)

Although infection is highest among patients with chronic GVHD, risk of infection in patients without chronic GVHD is still 20 times higher than reported in the general population. About a quarter of patients remain on IST beyond 3 years post allo-HCT, especially older adults, and late infections contribute to the significant morbidity and mortality after transplantation.\(^{10,28}\)

**Management approach**

In general, allogeneic HCT survivors require a lower threshold for evaluation and treatment of potential infections than the general population, even if normal neutrophil and lymphocyte counts are present, and especially in patients with chronic GVHD. Immune reconstitution takes 1-2 years and is never complete in some patients, so that minor infections may become serious quickly. Consultation with Infectious Diseases may be helpful to ensure that the full spectrum of potential pathogens is considered, especially if specialized testing is needed. If a patient with a prior history of allogeneic transplantation develops a serious infection, broad empiric coverage for both typical (pneumococcus, hemophilus, meningococcus) and atypical infections should be used pending identification of an organism.

Reactivation of varicella zoster virus (VZV) is the most frequent late viral infection, but other viruses can also reactivate and cause disease. Patients previously exposed to hepatitis B and C may reactivate and cause liver function abnormalities, especially as immunosuppression is tapered. Hepatology follow-up is recommended for these patients. Cytomegalovirus may reactivate late, especially if high dose steroids are
used for treatment of GVHD. Many transplant centers recommend that patients with chronic GVHD continue prophylaxis for Pneumocystis jiroveci pneumonia (PJP) and encapsulated organisms, and many also continue antiviral and antifungal prophylaxis until immunosuppression is discontinued.

**Vaccinations**

Vaccination is a potentially important strategy for reducing the risk for vaccine-preventable infections after HCT, although antibody response is often suboptimal.\(^{29,30}\) In our experience poor immune response to PPV23 was seen in all patient groups including survivors beyond 5 years post allo-HCT. This correlated with increased risk of recurrent bacterial infections and re-hospitalization in long-term survivors.\(^{31}\) About 20-50% of patients remain on IST beyond 3 years after allo-HCT with loss of protective vaccination titers if recipients are not re-immunized.

**Management approach**

We recommend starting immunizations with inactivated or killed vaccines in all eligible patients between 6-12 months after transplant, under the premise that there is little to lose, and some may mount effective responses. Post-HCT vaccination guidelines have recently been published.\(^{29,30}\) Our policy is to vaccinate for pneumococcus, hemophilus influenzae B, diphtheria, tetanus, acellular pertussis, meningococcus, inactivated polio, hepatitis A&B, influenza A and H1N1 within the first year post transplant preferably starting as early as 3-6 months post-HCT. Prevnar13 will be replacing Prevnar7.\(^{32,33}\) A controversial issue is whether to vaccinate patients with ongoing GVHD or on immunosuppressive treatment. While these patients should not receive live vaccines such as MMR, attenuated influenza or VZV vaccine, there is no evidence suggesting that inactivated vaccines exacerbate chronic GVHD, although they may fail to mount an immune response. If immunizations are delayed, it is important to reassess eligibility for vaccination at a later time. If a patient fails to generate an effective antibody titer to an initial series of immunizations, we usually repeat the vaccination series at least once more unless contraindicated.

All household contacts should also get yearly influenza vaccinations. Children of patients may receive most recommended vaccinations although inactivated polio is preferable over oral polio vaccine; exposure (bystander) to children who have had a recent live vaccination is safe considering no transmission reported after allo-HCT but precautions should be exercised by avoiding direct care-giving for 2-4 weeks. Patients who are exposed to known cases of hemophilus influenza B, pertussis, influenza A, varicella zoster virus, hepatitis B or tuberculosis should be considered for short-term prophylaxis.

**Pulmonary complications**
Obstructive pulmonary function abnormalities have been linked with chronic GVHD in long term survivors after allo-HCT, and noninfectious pulmonary deaths account for a significant proportion of non-relapse mortality. Lifetime risk of chronic pulmonary dysfunction ranges from 30 to 60%, and a forced expiratory volume in 1 second (FEV1) decline of 5% per year is associated with significant attributable late mortality rates of 9-40%.

Bronchiolitis obliterans syndrome (BOS) is a progressive, insidious, and often fatal lung alloreaction after allo-HCT. Clinical data suggest that inflammatory conditions such as viral infections, recurrent aspiration (gastroesophageal reflux disease), and chemoradiotherapy conditioning may also play a role in the pathogenesis of BOS. Unfortunately, the survival and treatment of patients with BOS have not improved over the last 20 years. Clark et al. reported a 3-year mortality rate of 65% in their patients with BOS accompanying chronic GVHD.

Restrictive changes are less common but may be due to extrinsic causes such as muscle weakness from prolonged steroid treatment, pulmonary fibrosis or sclerotic chronic GVHD involving the thorax. Reduction in diffusing capacity of carbon monoxide (DLCO) is common and often of unclear etiology. Bronchiolitis obliterans organizing pneumonia (BOOP), recently renamed cryptogenic organizing pneumonia (COP), is a rare late complication that can cause both restrictive changes and decreased DLCO.

**Management approach**

Because chronic pulmonary dysfunction can be insidious, we routinely perform pulmonary function tests at three and 12 months after transplant or earlier if a patient develops new unexplained symptoms. If results show a decline or if the patient is diagnosed with chronic GVHD, then we perform more frequent testing. We do not routinely perform chest x-rays or chest CTs unless specifically indicated to evaluate or follow a known process.

The initial workup for a patient with new onset air flow obstruction should include: a complete set of pulmonary function tests (PFT), inspiratory and high resolution expiratory chest CT, comprehensive infectious disease evaluation and a thorough chronic GVHD evaluation. Echocardiogram to assess pulmonary artery pressures and a 6-minute walk evaluation may also be helpful to rule out other diagnoses and assess for oxygenation status. Because histological confirmation is invasive and can be obtained in only a limited number of patients, BOS following allo-HCT is usually a clinical diagnosis.

If BOS is diagnosed, we administer systemic steroids using a similar dose regimen as for chronic GVHD. Prophylaxis for VZV, PJP, and encapsulated bacterial infections is continued. We also start inhaled
steroids and azithromycin 250 mg 3 days a week based on the low toxicity of the treatments and some reported benefits in lung transplant recipients.\textsuperscript{43,44} Azithromycin has anti-inflammatory, anti-microbial and gastrointestinal pro-motility properties. It can inhibit interleukin (IL)-8–associated inflammation, suppress infections and prevent gastroesophageal reflux, which have all been thought to contribute to BOS. Other agents that are used in chronic GVHD treatment are also used for BOS. Once significant lung impairment has occurred, improvement is seen in only a minority of the patients, and a realistic goal of treatment is to stop further decline. Patients with severe pulmonary insufficiency should be referred to pulmonary rehabilitation.

Patients with restrictive lung disease or decreased DLCO (generally below 40% predicted) are at risk for desaturation with exertion or at low oxygen tensions (high altitudes, airplane travel) and should be counseled to use caution in these circumstances.

**Diabetes mellitus**

Cross-sectional and retrospective studies have reported the prevalence of diabetes mellitus to be 7.6 to 13.1% after allo-HCT.\textsuperscript{45-47} Higher rates are reported in the first 1-2 years after transplant.

*Management approach*

No formal guidelines for monitoring for diabetes in post-HCT patients presently exist. However, monitoring fasting blood sugar when IST agents with potential impact on glycemia are added has been recommended.\textsuperscript{45} Patients with longstanding diabetes require regular monitoring for microvascular complications such as retinopathy, nephropathy and neuropathy, as well as blood pressure to goal <130/80 mm Hg. Diabetes is a cardiovascular risk equivalent similar to peripheral vascular disease, cerebrovascular accident, abdominal aortic aneurysm and presence of multiple risk factors (absolute risk in 10 years >20%) which is associated with high risk for subsequent cardiovascular events.

Although strict diet and exercise regimens may be difficult in patients, appropriate dietary and exercise counseling should be pursued in long-term survivors before insulin or oral hypoglycemic agent therapy is instituted. Insulin lacks drug interactions and can be customized to each patient’s daily needs, so it is the preferred agent for short term use or in a medically unstable patient. Sulfonylureas, metformin, and sitagliptin may be used in patients who can be managed with oral medications when there is no major contraindication.\textsuperscript{45} In most stable patients without anemia, hemoglobin variant or recent transfusions, a hemoglobin A1c goal of <7.0% with minimal hypoglycemia is an appropriate target.

**Cardiovascular disease**
Dyslipidemia, hypertension, diabetes and chronic kidney disease are associated with cardiovascular disease (CVD) and increased post-transplant, perhaps due to endothelial damage induced by GVHD, use of immunosuppressant agents, or other features inherent to HCT. Metabolic syndrome is a cluster of conditions associated with cardiovascular risk and has a reported incidence of 34-49% after HCT.

In one study having two or more cardiovascular risk factors after HCT was associated with a 5.2-fold increased risk of late CVD. The occurrence of vascular events at an earlier age than expected could not be explained solely by the established risk factors. The cumulative incidence of CVD approaches 23% at 25 years after HCT in high-risk populations, and the incidence is expected to continue to increase with longer time since HCT. An EBMT study provides preliminary evidence for an association between GVHD and the development of arterial disease.

Other cardiovascular complications resulting from transplant or prior chemotherapy can include cardiomyopathies, arrhythmias, or valvular dysfunction. These conditions are best managed by cardiologists and not discussed here.

Management approach

Management should focus mainly on preventative measures and controlling associated risk factors. Cardiovascular symptoms should be reviewed regularly and appropriate evaluations pursued based on acute symptoms or when cardiovascular risk factors are present for an extended period. Although we have a low threshold to perform an echocardiogram or functional testing in symptomatic patients, we do not perform screening in the absence of symptoms unless a patient has received high dose mediastinal or chest radiation.

Education and counseling of patients are crucial components of promoting health in HCT populations at risk of delayed CVD. Patients should be encouraged to reduce modifiable risk factors such as obesity, smoking, hypertension, and dyslipidemia. Proper management of cardiovascular risk factors has been shown to reduce the risk of cardiovascular events and improve survival in the non-HCT population, and could help reduce morbidity and mortality in HCT survivors.

Dyslipidemia

Prevalence of dyslipidemia at long-term followup ranges from 8.9% to 39%. Primary dyslipidemias can occur in HCT patients, and use of glucocorticoids, sirolimus, and calcineurin inhibitors can induce
dyslipidemia. Recommendations for monitoring and use of tools for risk assessment, lipid goals, and treatment of dyslipidemia have recently been reviewed.48

Management approach

Fasting lipid levels should be checked at least annually if patients are receiving immunosuppression, have chronic GVHD or have a previous abnormal lipid profile. More frequent testing may be necessary if a patient is started on a drug known to affect lipid metabolism, such as sirolimus, or had previous abnormal results. If a patient is off immunosuppression with a normal profile, then testing frequency may revert to general population guidelines.

In the absence of further data, we suggest using the NCEP ATP III guidelines but considering allo-HCT in itself to be a cardiac risk factor similar to hypertension, hyperlipidemia, advancing age, smoking and family history of cardiovascular disease, given evidence that HCT recipients have a 10-year incidence of cardiovascular disease of >10%. LDL-C levels are the primary treatment target, with the target level determined by the patient’s overall risk profile. Patients with 2 or more risk factors have moderate risk with an LDL-C goal of < 130 mg/dL. LDL-C goal should be < 160 mg/dL in low-risk adults (one or fewer risk factors).

For allo-HCT survivors at low to moderate risk, the decision to initiate drug therapy should be based on severity of hyperlipidemia and potential mitigating factors, such as risks of drug therapy, and whether discontinuation of any inciting factors such as sirolimus is anticipated. In addition to LDL-C, elevated triglycerides may contribute to CAD risk; thus if triglycerides remain elevated after LDL-C treatment, they can also be considered a treatment target. Triglycerides > 500 mg/dL should be treated in order to prevent pancreatitis.

HMG-CoA-reductase inhibitors (statins) have the strongest evidence for reduction in cardiovascular outcomes as well as the most potent effects on LDL-C. Omega-3-fatty acids have no significant drug interactions and can lower triglycerides by 35-45% in sufficient doses. Fibric acid derivatives (fenofibrate or gemfibrozil) may be required for treatment of more severe hypertriglyceridemia. Side effects of fibric acid derivatives can include elevations of liver enzymes, myopathy, and renal dysfunction; caution should be used when combining these agents with calcineurin inhibitors or statins.

A fasting lipid panel should be repeated 1-3 months after any change in lipid lowering agents to assess the effectiveness of the change.

Hypertension
Management

Transplant survivorship guidelines recommend checking blood pressure at every clinic visit.\textsuperscript{57} Hypertension in long term survivors should be diagnosed and treated according to Joint National Committee (JNC 7) guidelines.\textsuperscript{58} In addition to its cardiovascular risk contribution, post-transplant hypertension is associated with chronic kidney disease after HCT.\textsuperscript{50} Choice of antihypertensive agent is made based on co-morbid diseases\textsuperscript{58,59} and individual agents’ side effect profiles. Angiotensin-receptor blockers and angiotensin-converting enzyme inhibitors are generally preferred in those patients with chronic kidney disease or diabetes because of their renal protective effects. Fluid balance, potassium and renal function should be monitored after initiation.

Thyroid dysfunction

Long-term prevalence of hypothyroidism appears to be approximately 20-40%,\textsuperscript{60-62} possibly higher in survivors of childhood HCT. In addition to affecting quality of life, untreated hypothyroidism can have cardiac and metabolic sequelae. Hyperthyroidism is less common in post-HCT patients but has been described as a possible autoimmune transfer phenomenon.\textsuperscript{63}

Management approach

Transplant survivorship guidelines recommend checking thyroid function tests annually or when symptoms are present.\textsuperscript{57} Testing for TSH and free T4 allows assessment of the pituitary-thyroid axis. Treatment should be initiated in cases of overt primary or central hypothyroidism. For subclinical hypothyroidism with mild TSH elevation (e.g. < 10 IU/ml), it is reasonable to repeat labs in 2-3 months before starting treatment since such elevations may be transient. Underlying autoimmune thyroid disease with positive thyroid antibodies should increase likelihood of replacement therapy for subclinical hypothyroidism. Therapeutic replacement dosing is approximately 1.6 micrograms of levothyroxine per kg of body weight; however, a lower initial dose may be used. TSH and free T4 should be checked 6-8 weeks after dose initiation or changes, and replacement titrated to keep TSH closer to the lower limits of normal, as evidence suggests the majority of individuals without thyroid disease have a TSH within this range.\textsuperscript{64} Bone loss and arrhythmias are the major risks of overtreatment.

Hypogonadism

Hypogonadism is very common after transplant, particularly in women. Major indications for treatment of adult hypogonadism include maintenance of bone density and prevention of symptoms in men and pre-menopausal-aged women. Men are more likely to have damage to the germ cell epithelium resulting in
reduced fertility but may retain normal testosterone production. Almost all women will have some gonadal dysfunction after high intensity conditioning. Infertility is common and reproductive endocrinology consultation should be obtained when indicated. There are reports of recovery of spermatogenesis in about 25% of young patients surviving beyond 10 years post-HCT, even after TBI dose >1000 cGY.65;66

**Male**

Men should be tested for hypogonadism if suggestive symptoms of erectile dysfunction, low libido, fatigue or bone loss are present. Some centers routinely measure testosterone at one year after transplant, particularly if men are receiving steroids. Total testosterone is a reasonable initial test, followed by a morning total or free testosterone if total testosterone is abnormal. Leutinizing hormone measurement will help determine primary vs. secondary/central hypogonadism. If low testosterone is confirmed on two measurements, treatment may be initiated with a transdermal gel, patch daily or intramuscular injections every 2 weeks.67 We prefer gel and patch formulations for more physiologic replacement because injections are more likely to cause side effects such as mood swings and erythrocytosis, and it is more difficult to evaluate adequacy of therapy due to peaks and troughs after injections. Oral preparations of testosterone can be hepatotoxic and should be avoided. Prostate cancer and male breast cancer are the two absolute contraindications to testosterone therapy. Hematocrit, prostate-specific-antigen, and digital rectal exam should be measured at baseline, every 3 to 6 months for the first year of treatment, then annually. The goal of therapy is a testosterone level within the normal range and improvement in symptoms. Testosterone therapy will suppress spermatogenesis67 and may impact fertility treatment.

**Female**

Primary ovarian insufficiency or failure is diagnosed when two serum follicle stimulating hormone (FSH) measurements are in the menopausal range, at least one month apart. Estradiol levels may be variable. Amenorrhea with low FSH and low estradiol suggest central hypogonadism. Patients making no estrogen will have atrophic endometrium, but patients with ovarian insufficiency may have variable estradiol levels, so protection from endometrial hyperplasia should still be considered. For physiologic replacement, 100 mcg/day estradiol by transdermal patch appears to achieve levels of serum estradiol in the normal range.68 Some women may achieve adequate levels and normal menstrual cycles on a lower patch dosage. Women with an intact uterus should have cyclic medroxyprogesterone added (10 mg/day for 12 days of each menstrual cycle) to induce menstruation and prevent endometrial hyperplasia.68 Combination oral contraceptives may also be used. Transdermal estrogen may carry lower risk of venous thromboembolism. Estrogen-progesterone replacement should be stopped when patients reach an age of
normal menopause due to the increased risk of breast cancer and other adverse events observed with routine post-menopausal replacement (http://www.nhlbi.nih.gov/whi/), especially since rates of breast cancer are increased after HCT.\textsuperscript{18} Estrogen-progesterone therapy is contraindicated in patients with history of stroke, venous thromboembolism, severe hypertriglyceridemia, active liver disease, undiagnosed abnormal uterine bleeding, or estrogen-dependent tumors such as breast cancer.

**Iron Overload**

Iron overload is common after HCT and may be associated with liver toxicity and organ dysfunction.\textsuperscript{70-72} In heavily transfused patients (e.g. thalassemia, myelodysplastic syndrome, severe aplastic anemia, poor red cell engraftment), assessment of iron overload should occur periodically. Ferritin is the most sensitive screening test, although it may be elevated due to hepatic inflammation or as an acute phase reactant. Liver MRI and liver biopsy are sometimes pursued to provide quantification of iron stores. If ferritin is greater than 2500 ng/ml or hepatic iron measured or estimated is greater than 7 mg/g dry weight, we evaluate the patient for therapeutic phlebotomy or chelation with desferoxamine or desferasirox.\textsuperscript{73} Chelating agents can cause gastrointestinal toxicity, renal insufficiency, and ocular and auditory abnormalities. Phlebotomy requires adequate erythropoiesis and a hematocrit greater than 38% in order to remove 1 unit every 6-8 weeks, keeping hematocrit > 35%. With both methods of iron removal, ferritin is monitored every 3 months with a goal of achieving < 500-1000 ng/ml.

**Bone Loss**

Loss of bone density is common after transplant and begins early. More than half of long term survivors assessed with DEXA develops osteopenia (T-score on bone densitometry <-1 and \(\geq\) -2.5) or osteoporosis (T-score <-2.5) following allo-HCT with increased risk when chronic GVHD is present.\textsuperscript{74-77} Factors potentially contributing to bone loss in this population include hypogonadism, direct damage to osteoprogenitor cells, glucocorticoid exposure, use of calcineurin inhibitors, secondary hyperparathyroidism, hyperthyroidism, and calcium and/or vitamin D deficiency. Reduction in steroid doses or steroid sparing therapy should be considered when possible to prevent bone loss.

**Management approach**

Transplant survivorship guidelines recommend checking bone mineral densitometry within one year of transplant in women or anyone treated with prolonged corticosteroids or calcineurin inhibitors.\textsuperscript{57} We perform a DEXA at 3 months and one year if patients are exposed to steroids.
For prophylaxis, elemental calcium intake of 1000-1500 mg/day in divided doses as well as vitamin D at 1000 IU/day should be initiated in all patients. We recommend measuring 25-hydroxyvitamin D levels and repleting with ergocalciferol 50,000 IU one or more times weekly if levels are < 30 ng/mL, rechecking levels in several weeks to assess for adequate replacement. Gastrointestinal GVHD may interfere with absorption of supplements. Calcium should be given with food to maximize absorption, and calcium citrate should be used in patients on antacids or proton-pump inhibitors. Weight-bearing exercise should be encouraged as tolerated. While hypogonadism should be treated when present, this alone will not prevent bone loss.77

Bisphosphonates are the mainstay of treatment for established osteoporosis. If oral bisphosphonates are not tolerated because of gastrointestinal GVHD or esophageal/reflux symptoms, intravenous (IV) formulations may be used but are contraindicated if creatinine clearance is <30-35. For example, intravenous zoledronic acid (Reclast®) is approved for once-yearly administration in a dose of 5 mg annually for treatment or every two years for prevention of osteoporosis. Zoledronic acid (Zometa®) at a 4 mg dose monthly for 3 months has also been used in trials with HCT patients, with increase in lumbar spine and femoral neck bone mineral density (BMD).77 Osteonecrosis of the jaw is a rare but serious side effect of bisphosphonates. Cases of atypical (e.g. subtrochanteric and diaphyseal femur) fractures have been reported in patients on long-term bisphosphonates but the risk is low and it is controversial whether bisphosphate therapy was the cause.78

If normal BMD is documented after transplant in patients without ongoing exposure to risk factors, then repeat densitometry at 2 or more years is suggested. In patients on treatment for osteoporosis or osteopenia, monitoring every 1-2 years is recommended. Duration of bisphosphonate therapy remains an area of uncertainty with no randomized controlled trial data. A drug holiday may be considered after approximately five years of therapy.

Avascular necrosis (AVN)

Avascular necrosis is a disabling long term complication after allo-HCT and reported to occur in 4% to 19%. It can lead to joint pain, bone destruction, and loss of function with significant impairment in quality of life.8,9,79-81 The mean time from transplantation to AVN is 1-2 years post-HCT, and pain and limited activity is usually the first sign. The hip is the most affected site in a majority of cases, but multiple site involvement is common.

Management approach
Diagnosis can be made using magnetic resonance imaging, and early treatment of AVN can decrease its morbidity, although the majority of patients eventually require surgical intervention. With mild-moderate symptoms, core decompression may delay replacement surgery; however, in obese patients or those with severe symptoms, early surgical intervention is well tolerated and should be pursued. Patients may need to temporarily use a wheelchair or decrease weight-bearing activities when experiencing an exacerbation of pain. In addition to pain management and surgery, we also recommend DEXA scanning to evaluate for bone loss that would require bisphosphonates (discussed above in bone loss).

**Long term renal complications**

Chronic kidney disease (CKD) in long term survivors after HCT occurs with a reported prevalence from 4-89% depending on the definition used. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative defines CKD as a GFR of less than 60 ml/min/1.73 m2 for three or more months, with or without kidney damage.

*Management approach*

Published recommendations for transplant survivors include assessment of blood urea nitrogen, creatinine, calculation of glomerular filtration rate, and urine protein analysis (urine microalbumin) at regular intervals, more frequently in patients with chronic GVHD and at least annually in all patients after HCT. Renal biopsy should be considered in cases with unclear CKD after transplantation. Detection of CKD is important, because these patients have adverse outcomes, such as kidney failure, cardiovascular disease, and premature death, which can be prevented or delayed by interventions. Angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) can help to reduce inflammation and inflammatory markers and are the treatment of choice for hypertension and CKD.

**Keratoconjunctivitis sicca syndrome and cataracts**

Late eye complications like keratoconjunctivitis sicca syndrome and early cataract formation can occur after allo-HCT and greatly affect quality of life.

*Management approach*

Published recommendations include annual evaluation of visual history and symptoms, with ophthalmologic exam if patients are symptomatic or have abnormal findings. Cataracts can be managed surgically similar to non-transplant individuals even in the setting of dry eyes. The keratoconjunctivitis sicca syndrome causes eye dryness and irritation, and often occurs as part of the chronic GVHD syndrome. Referral to an ophthalmologist is recommended. Frequent topical lubricants and nighttime gels...
can relieve symptoms. Topical immunosuppressive agents such as steroids or cyclosporine may be helpful. Autologous serum eye drops prepared locally can help in some refractory patients. Special contact lenses such as the Scleral Lens, a special ventilated gas permeable contact lens that creates a space over the cornea that is filled with artificial tears, can relieve symptoms in severe cases.

Summary

The rapidly growing population of allo-HCT survivors creates an obligation to educate patients and physicians about the late complications observed in patients after this therapy. Higher than average rates of second malignancies and cardiopulmonary, infectious, endocrine, and renal diseases, and bone loss or avascular necrosis suggest that this population requires more frequent screening and earlier interventions than the general population. Since many transplant survivors are cared for by their hematologist-oncologists, internists, or primary care physicians rather than the transplant center, we have tried to summarize the current thinking about best screening and treatment approaches to these common complications. Since we are not able to cover all potential late complications of allo-HCT, practitioners caring for these patients are encouraged to contact the transplant center for additional guidance.

Authorship

B.N.S., S.J.L designed the review; and B.N.S., M.L.G, S.J., S.J.L. each contributed to the writing of the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Acknowledgment

The authors wish to thank Dr. Mary Flowers for helpful comments on the manuscript.

Reference List


12. Couriel D, Carpenter PA, Cutler C et al. Ancillary therapy and supportive care of chronic graft-versus-host disease: national institutes of health consensus development project on criteria for


64. McDermott MT, Haugen BR, Lezotte DC, Seggelke S, Ridgway EC. Management practices among primary care physicians and thyroid specialists in the care of hypothyroid patients. Thyroid. 2001;11(8):757-764.


How I treat late effects in adults after allogeneic stem cell transplantation

Bipin N Savani, Michelle L Griffith, Shubhada Jagasia and Stephanie J Lee

Advance online articles have been peer reviewed and accepted for publication but have not yet appeared in the paper journal (edited, typeset versions may be posted when available prior to final publication). Advance online articles are citable and establish publication priority; they are indexed by PubMed from initial publication. Citations to Advance online articles must include digital object identifier (DOIs) and date of initial publication.