Late effects of blood and marrow transplantation

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ABSTRACT

Hematopoietic cell transplantation is a curative treatment for a variety of hematologic diseases. Advances in transplantation technology have reduced early transplant-related mortality and expanded application of transplantation to older patients and to a wider variety of diseases. Management of late effects after transplantation is increasingly important for a growing number of long-term survivors that is estimated to be half a million worldwide. Many studies have shown that transplant survivors suffer from significant late effects that adversely affect morbidity, mortality, working status and quality of life. Late effects include diseases of the cardiovascular, pulmonary, and endocrine systems, dysfunction of the thyroid gland, gonads, liver and kidneys, infertility, iron overload, bone diseases, infection, solid cancer, and neuropsychological effects. The leading causes of late mortality include recurrent malignancy, lung diseases, infection, secondary cancers and chronic graft-*versus*-host disease. The aim of this review is to facilitate better care of adult transplant survivors by summarizing accumulated evidence, new insights, and practical information about individual late effects. Further research is needed to understand the biology of late effects allowing better prevention and treatment strategies to be developed.

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Introduction

Hematopoietic cell transplantation (HCT) is a curative treatment for a variety of hematologic diseases.[1] The safety of HCT has improved over the decades,[2] indications for HCT have expanded to older patients,[3] and almost all patients are able to find suitable allogeneic donors by the growing use of cord blood[4] and haploidentical transplantation.[5] These current conditions have contributed to a growing number of HCT survivors, estimated to be half a million worldwide.[6]

Patients who are disease-free at two or five years after HCT have a greater than 80% subsequent 10-year survival rate,[7-10] but many studies show that HCT survivors suffer from significant late effects that adversely affect morbidity, mortality, working status and quality of life.[7-13] A prospective observational study of 1022 survivors who underwent HCT between 1974 and 1998 showed that 66% of the survivors had at least one chronic condition and 18% had severe or life-threatening conditions.[14] A retrospective study of 1087 contemporary survivors also showed that the cumulative incidence of any non-malignant late effect at five years after HCT was 45% among autologous and 79% among allogeneic recipients, and 2.5% of autologous and 26% of allogeneic recipients had three or more late effects.[15] Life expectancy among 5-year survivors remained 30% lower compared with the general population, regardless of their current ages and years since HCT.[9] The leading causes of excess deaths in 5-year survivors included secondary malignancies (27%) and recurrent disease (14%), followed by infections (12%), chronic graft-*versus*-host disease (GvHD) (11%), cardiovascular diseases (11%), and respiratory diseases (7%).[9]

The aim of this review is to facilitate better care of adult HCT survivors by summarizing accumulated evidence, new insights, and practical information about individual late effects (Figure 1). Recurrent disease and chronic GvHD are not discussed and readers are referred to other reviews.[16-20]

Cardiovascular diseases

Cardiovascular diseases (CVD) after HCT include cardiomyopathy, congestive heart failure, valvular dysfunction, arrhythmia, pericarditis, and coronary artery disease.[21] Their cumulative incidences were 5%-10% at ten years after HCT,[22-24] accounting for 2%-11% of mortality among long-term survivors.[8,9,25] The incidence of CVD and its associated mortality were 1.4-3.5-fold higher compared with the general population.[8,9,24,25] HCT survivors are more likely to have conventional risk factors such as dyslipidemia and diabetes than the general population.[26] Early diagnosis and treatment of modifiable risk factors is important. We usually treat hypertension more than 140/90 mmHg on 2 separate visits or more than 130/80 mmHg for patients with diabetes or renal disease.[27] The first step is lifestyle modification including weight reduction, dietary sodium reduction and regular physical activity, followed by initiating antihypertensive drugs such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs).

Anthracycline exposure and chest radiation are the major risk factors for CVD after HCT.[21] Several studies showed that dexrazoxane, ACE inhibitors, ARBs and beta-blockers can prevent anthracycline-related cardiomyopathy in the non-HCT setting.[28-32] Once cardiomyopathy is established, it is important to initiate appropriate treatment. ACE inhibitors and beta-blockers have been effective in improving left ventricular function.[33]

Pulmonary diseases

Non-infectious late complications of the lung include bronchiolitis obliterans syndrome (BOS), cryptogenic organizing pneumonia (COP) and pulmonary hypertension. BOS represents chronic GvHD of the lung, and is characterized by the new onset of fixed airflow obstruction after allogeneic HCT.[34] According to the strict 2005 National Institutes of Health (NIH) diagnostic criteria for chronic GvHD, incidence of BOS was 5.5% and its prevalence was 15% among patients with chronic GvHD.[35] Symptoms of BOS include dyspnea on exertion, cough and wheezing, but early BOS may be asymptomatic until significant lung function is lost.[36] One study showed rapid decline in %FEV1 during the six months before BOS diagnosis, with a lower %FEV1 at diagnosis associated with worse survival.[37] In our practice, we perform pulmonary function tests every three months including %FEV1 and FEV1/FVC among patients with active chronic GvHD. When testing shows significant new airflow obstruction, we repeat testing every month until stability is confirmed.[38] Plasma matrix metalloproteinase 3 levels[39] and parametric response mapping from CT scans[40] might be useful diagnostic tests for BOS but these have not yet entered clinical practice. Standard treatment of BOS is prednisone at 1 mg/kg per day, followed by a taper to reach a lower, alternate-day regimen.[38] A multicenter prospective study showed that addition of FAM (inhaled fluticasone propionate at 440 μg twice a day,

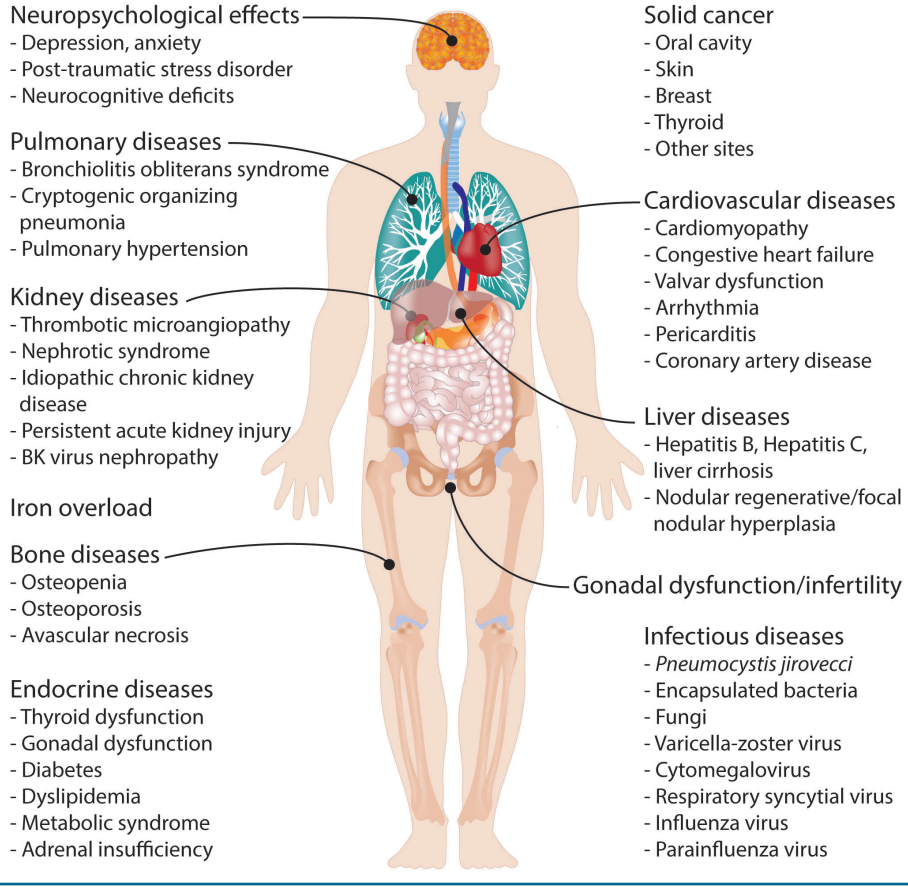

Figure 1. Late effects of blood and marrow transplantation.

azithromycin at 250 mg taken 3 days per week, and montelukast at 10 mg nightly) to prednisone treatment stabilized pulmonary function in 70% of patients with newly diagnosed BOS and permitted systemic steroid exposure to be reduced.[41]

Cryptogenic organizing pneumonia is a disorder involving bronchioles, alveolar ducts, and alveoli, the lumen of which become filled with buds of granulation tissue consisting of fibroblasts.[42] Clinical symptoms include dry cough, shortness of breath, and fever. Bronchoalveolar lavage is performed to exclude infection. Lung biopsy is required for definitive diagnosis, but an empiric diagnosis is often based on radiographic findings of diffuse, peripheral, fluffy infiltrates consistent with airspace consolidation. Pulmonary function testing shows restrictive changes and low diffusing capacity of the lungs for carbon monoxide. The incidence of COP is 2%-10%,[43,44] and it is strongly associated with acute and chronic GvHD.[45] COP usually responds within 5-7 days to prednisone at 1 mg/kg per day, which is continued for one month followed by a slow taper over five months because COP can often recur. Small case series suggest potential benefits of macrolides for treatment of COP.[46]

Pulmonary hypertension is an uncommon but potentially fatal complication after HCT, with a reported prevalence of 2.4%.[47] The most common symptoms are hypoxia, tachypnea, dyspnea, and acute respiratory failure,[48] and if untreated, pulmonary hypertension can result in a progressive increase in pulmonary vascular resistance, right ventricular failure and death. Since initial symptoms are non-specific, it is likely to be underdiagnosed after HCT. Although cardiac catheterization is the gold standard for diagnosis of pulmonary hypertension, high-resolution chest computed tomography and echocardiography are non-invasive and useful diagnostic modalities. The most common types are pulmonary arterial hypertension and pulmonary veno-occlusive disease, sometimes associated with transplant-associated microangiopathy and inherited or acquired hemolytic anemia.[48] First-line therapies are supplemental oxygen and phosphodiesterase-5 inhibitors, followed by inhaled nitric oxide, diuretics, bipyridine inotropes and after-load reducing agents.[48]

Endocrine diseases

Major late effects in the endocrine system include thyroid dysfunction, diabetes, dyslipidemia, and adrenal insufficiency. Hypothyroidism occurs in 30% of patients by 25 years after HCT.[49] Risk factors include age under ten years, conditioning containing radiation, busulfan or cyclophosphamide, and hematologic malignancies.[49,50] The international guidelines recommend checking serum thyroid-stimulating hormone and free thyroxine levels every year.[21] For patients who received radiolabeled iodine antibody therapy, thyroid function should be checked earlier starting at three and six months after HCT, and other times as clinically indicated. Standard criteria are used to initiate replacement therapy for hypothyroidism. Some patients develop hyperthyroidism after HCT as a rare complication.[51]

Diabetes occurs in 8%-41% of patients after allogeneic HCT and in 3% of patients after autologous HCT.[15,52,53] Its incidence after allogeneic HCT is 3.65 times higher compared with their siblings.[54] Initial treatment is therapeutic lifestyle counseling, but many patients require hypoglycemic agents or insulin.

Dyslipidemia occurs in 9%-61% of HCT survivors.[53,55] Despite no established consensus for management of dyslipidemia after HCT, our practice is to initiate therapeutic lifestyle counseling followed by statin therapy when LDL cholesterol exceeds 130-190 mg/dL according to the estimated risk of CVD, based on the National Cholesterol Education Program Adult Treatment Panel III guidelines[56] and the recently suggested approach after allogeneic HCT.[57] The 2013 ACC/AHA guidelines do not specify the targeted levels for LDL cholesterol, and addition of statin therapy is based on calculated risk for future cardiovascular events.[58] Addition of omega-3-acid ethyl esters or fibrate is considered when fasting triglycerides exceed 200-499 mg/dL.

Adrenal insufficiency occurs in 13% of patients after allogeneic HCT and 1% of patients after autologous HCT,[15] and can be confirmed by a cortisol-stimulation test. Once adrenal insufficiency is diagnosed, physiological glucocorticoid replacement and a very slow terminal taper is needed. Patients should carry notification that they have adrenal insufficiency to alert emergency medical providers. For chronic GvHD therapy, the risk of adrenal insufficiency is lower with alternate-day administration of corticosteroids than with daily dosing,[59] although patients with brittle diabetes need daily dosing to allow for optimal glucose control.

Male gonadal dysfunction and infertility

Hypogonadism is common after HCT. Impaired spermatogenesis, erectile dysfunction, low testosterone, and low libido occur in male patients. Erectile dysfunction and low libido have been associated with both physical and psychosocial factors.[60,61] Testosterone replacement may be considered for patients with low testosterone levels and has improved sexual function, libido and bone mass, although monitoring prostate-specific antigen and testosterone levels is necessary.[62,63] Azoospermia occurred in 70% of male patients, and spermatogenesis recovered in 90% of patients conditioned with cyclophosphamide alone, in 50% of patients conditioned with cyclophosphamide plus busulfan or thiotepa, and in 17% of patients conditioned with total body irradiation (TBI).[64] Semen banking or cryopreservation of testicular tissue should be discussed before HCT with patients desiring fertility.

Female gonadal dysfunction, infertility and pregnancy

Ovarian insufficiency, vaginal changes and low libido occur in female patients. A historical study showed that ovarian failure occurred in more than 90% of female patients after HCT and recovered in 92% of patients conditioned with cyclophosphamide alone, but only in 24% of patients conditioned with cyclophosphamide and TBI.[65] A pilot study showed that only 10% of patients had ovarian failure after reduced-intensity allogeneic HCT.[66] The use of hormone replacement therapy for premature ovarian failure should be individualized based on the patient age, severity of menopausal symptoms, low bone density, risk of breast cancer, clotting predisposition and liver abnormalities.[67] Since efficacy of gonadotropin-releasing hormone agonists in preserving fertility in cancer patients is controversial,[68,69] cryopreservation of oocytes, ovarian tissue, or embryos should be discussed with patients desiring fertility.[70]

The largest study of pregnancy after HCT showed that

0.87% of patients or their partners had pregnancies after allogeneic HCT, and 0.36% of those after autologous HCT.[71] We generally recommend that women wait 2-5 years after HCT before attempting conception since rates of relapse are generally highest in the first two years after HCT. Another concern is the theoretical risk of recurrent malignancy because of disturbance of the graft-*versus*-leukemia effect, and some cases of recurrent chronic myeloid leukemia after conception have been reported.[71] Pregnancy outcomes are generally good with no increase in the risk of fetal malformations, although these pregnancies are considered high risk because of higher maternal risks of pregnancy complications.[71]

Iron overload

Iron overload is rare after autologous HCT[72] but common after allogeneic HCT.[73,74] Previous prospective studies showed that 30%-60% of long-term survivors of allogeneic HCT had elevated serum ferritin levels and 25%-50% had elevated liver iron concentration on T2* magnetic resonance imaging (MRI).[73,74] Since serum ferritin does not specifically reflect iron overload and can be elevated in hepatic and systemic inflammation, additional testing is required if the ferritin is elevated. We favor transferrin saturation, which is widely available and defined as the ratio of serum iron concentration divided by total iron-binding capacity.[75] Normal transferrin saturation is less than 50% in males and less than 45% in females. Patients with iron overload usually have saturation more than 60%. *HFE* genotyping is considered in patients with a family history of hemochromatosis and in patients of Northern or Western European ethnicity. When saturation is not elevated, other etiologies for an elevated ferritin including inflammation, metabolic syndrome, and alcoholism should be ruled out. The most accurate test of tissue iron concentration is liver biopsy, but the procedure is invasive and may cause serious complications. Thus, T2* MRI and other modalities (FerriScan and superconducting quantum interference device) have been increasingly used.[76] Importantly, liver tests are often normal among long-term survivors with iron overload, so hepatitis and GvHD should also be considered when results of liver tests are elevated.[77] Iron overload may cause cardiomyopathy. Studies of thalassemia patients showed that cardiomyopathy typically took more than ten years to be clinically evident,[78] and that many patients improved with intensive chelation therapy.[79] Although a prospective study and a meta-analysis showed no statistical association of liver iron concentration with mortality after allogeneic HCT,[80,81] our practice is to start phlebotomy of 5 mL/kg or 250-300 mL every 3-4 weeks as long as hematocrit is more than 35% until serum ferritin falls below 1000 ng/mL. Deferasirox, an oral chelating agent, is considered for patients with anemia precluding phlebotomy.

Liver diseases

Late liver diseases include chronic hepatitis B, chronic hepatitis C, liver cirrhosis, nodular regenerative hyperplasia and focal nodular hyperplasia.[77] Hepatitis B-infected patients have an increased risk of fulminant liver failure. One study reported a 35% risk of HBV reactivation after HCT even among patients with isolated anti-HBc antibodies, mostly during steroid treatment for GvHD.[82] Patients treated with anti-CD20 antibodies have an increased risk of HBV reactivation. Antiviral prophylaxis using entecavir or lamivudine will prevent almost all fulminant cases if initiated before the start of conditioning regimens in patients with positive blood HBV DNA levels.[83] Patients with latent HBV (i.e. anti-HBc$^+$/HBV DNA$^-$) should be monitored monthly with HBV DNA levels after HCT and antiviral treatment should be initiated when viremia is detected.[83]

Hepatitis C virus infection in HCT survivors almost always results in chronic hepatitis.[84,85] Typically, asymptomatic elevation of alanine aminotransferase occurs 2-4 months after HCT, coinciding with tapering of immunosuppressive medications. There may be little liver-related mortality in the first ten years after HCT,[84] but liver cirrhosis occurs later with a cumulative incidence of 4%-24% at 20 years.[85,86] A large retrospective study showed that hepatitis C-infected patients had an increased risk of 2-year non-relapse mortality due to hepatic problems and bacterial infection.[87] Antiviral therapy for HCV has not been given early after HCT, but may improve both oncological and hepatic outcomes after HCT.[88] Ribavirin and interferon-based therapy have been used for patients who have discontinued all immunosuppressive medications without active GvHD, but it can cause pancytopenia and GvHD. Recently, highly effective and well tolerated direct acting antiviral agents with more than 90% rates of sustained virological response have been developed, and interferon-free regimens are now the treatments of choice.[89,90]

Nodular regenerative hyperplasia is a rare liver condition characterized by a widespread benign transformation of the hepatic parenchyma into small regenerative nodules.[77] This process is usually asymptomatic unless portal hypertension develops. Focal nodular hyperplasia occurs in 12% of HCT survivors, and possibly reflects sinusoidal injury caused by myeloablative conditioning regimens.[91]

Kidney diseases

Chronic kidney disease (CKD) is defined as an elevated serum creatinine level, or a decreased glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2 for three months or longer.[92] CKD occurs in approximately 20% of HCT recipients.[93-95] There are three major etiologies of CKD after HCT: thrombotic microangiopathy (TMA), nephrotic syndrome and idiopathic CKD. Other etiologies include persistent acute kidney injury and BK virus nephropathy.[96] Whenever possible, renal biopsy should be considered to accurately diagnose the etiology of CKD and to provide appropriate management.[97]

Thrombotic microangiopathy occurs in 2%-21% of patients after HCT, and is characterized by renal dysfunction, thrombocytopenia, neurological dysfunction, hemolytic anemia with schistocytes, elevated lactate dehydrogenase and decreased haptoglobin.[98,99] Risk factors of TMA include TBI, calcineurin inhibitors, and acute and chronic GvHD.[100-102] TMA-related kidney injury often improves with tapering or stopping calcineurin inhibitors, but full renal function is rarely restored.[103] In some cases TMA did not improve until GvHD was treated.[104] Efficacy of plasma exchange is limited.[105]

Nephrotic syndrome occurs in 6%-8% of patients after allogeneic HCT.[106,107] Membranous nephropathy comprised 61% of cases, and minimal change disease comprised 22% of cases, with a median onset of 14 months and eight months after HCT, respectively.[108] Mechanisms of membranous nephropathy are thought to be formation of immune complexes through allo- or auto-antibodies

recognizing antigens expressed by the podocyte, while T cells are implicated with minimal change disease.[109] Nephrotic syndrome after HCT is often associated with chronic GvHD and tapering of immunosuppressive medications. Initial treatment is prednisone 1 mg/kg/day in addition to calcineurin inhibitors. Complete response was observed in 90% of patients with minimal change in disease, but only in 27% of patients with membranous nephropathy.[108] Refractory cases may be treated with rituximab or mycophenolate mofetil.[110]

Idiopathic CKD comprises most cases of CKD. Risk factors include acute GvHD, chronic GvHD, acute kidney injury, long-term use of calcineurin inhibitors and previous autologous HCT,[94,111] suggesting that GvHD, accompanying treatment and inflammatory conditions may have pathogenic roles in this entity. Associations of TBI with risk of CKD have been controversial.[94,112] ACE inhibitors and ARBs have been used to treat CKD and hypertension associated with CKD.[113]

Bone diseases

Late complications of bone include osteopenia, osteoporosis and avascular necrosis (AVN).[114] Osteoporosis has been reported in as many as 50% of HCT recipients.[115,116] The diagnoses of osteopenia and osteoporosis are made by measuring T-scores with dual-energy X-ray absorptiometry. A T-score between -1.0 and -2.5 indicates osteopenia, and a T-score less than -2.5 or presence of a fragility fracture indicates osteoporosis.[117] Multiple risk factors are implicated including chemotherapy, radiation, corticosteroids, calcineurin inhibitors, vitamin D deficiency, and gonadal failure.[116,118] Bone loss occurs within 6-12 months after HCT, and recovery of bone mineral density (BMD) begins from the lumber spine, followed by a slower recovery in the femoral neck. The use of corticosteroids is the strongest risk factor for osteoporosis. General preventative recommendations include adequate intake of calcium of 1200 mg per day or over and vitamin D of 1000 IU (25 μg) per day or over, regular weight-bearing exercise, and avoidance of smoking and excessive alcohol. Bisphosphonates are the primary treatment for bone loss.[119] Patients who are taking 5 mg or more daily prednisone-equivalent steroids for three months or more should have screening BMD tests for osteoporosis, and bisphosphonate treatment may be indicated until corticosteroid treatment is discontinued or for up to five years.[120] Second-line treatment includes calcitonin, raloxifene, denusomab, romosozumab, and blosozumab, though their reported use in HCT recipients is limited and adverse effects may be more prominent than with the bisphosphonates.

Avascular necrosis occurs in 4%-19% of HCT survivors with a cumulative incidence of 3%-10% at five years after HCT.[121,122] AVN causes severe bone pain and bone destruction, causing significant impairment in quality of life. AVN typically affects the femoral heads, but sometimes affects other joints such as the knee and shoulders.[21] Risk factors for AVN include corticosteroids, calcineurin inhibitors, older age and TBI conditioning.[114] When AVN is suspected, diagnostic MRI should be performed. Early involvement of an orthopedic specialist is important for management of AVN, including conservative treatment, joint-preserving surgery and joint replacement surgery.[21,114]

Infectious diseases

All HCT survivors have some degree of immunodeficiency, particularly during the first year after HCT.[123] If patients are able to stop immunosuppressive medications without GvHD or recurrent disease, many recover adequate immune function by one year after HCT. Patients with chronic GvHD, however, remain immunodeficient and have a high risk of infections. Common late infections are caused by *Pneumocystis jirovecii*, encapsulated bacteria, fungi, varicella-zoster virus (VZV), cytomegalovirus, and respiratory viruses. Patients may report more frequent episodes of upper respiratory infections and sinusitis.

All patients should receive prophylaxis against *Pneumocystis jirovecii* for at least one year after HCT or until 3-6 months after all immunosuppressive medication is discontinued, whichever occurs later. The preferred drug is trimethoprim-sulfamethoxazole, but dapsone or atovaquone could be substituted for patients who are allergic to or intolerant of trimethoprim-sulfamethoxazole.

In particular, patients with chronic GvHD are highly susceptible to encapsulated bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitidis* due to low levels of opsonizing antibodies, low $CD4^+$ T-cell counts, poor reticuloendothelial function and suppressive effects of immunosuppressive medications on phagocytosis. Vaccination against these bacteria is recommended.[124] Efficacy of vaccination in increasing antibody levels has been shown in several prospective studies.[125,126] Chemoprophylaxis is always recommended due to the unpredictable protection provided by vaccination. The first-line drug is trimethoprim-sulfamethoxazole, but if it is not tolerated, penicillin or azithromycin is substituted until 3-6 months after discontinuation of all immunosuppressive medications.

Invasive fungal infection occurs in 1% of patients after autologous HCT and in 6%-8% of patients after allogeneic HCT.[127] GvHD and long-term use of corticosteroids have been a major risk factor associated with onset of invasive fungal infection.[128] As recommended in the European guidelines, mold prophylaxis with posaconazole or voriconazole may be considered for patients with GvHD requiring high-dose corticosteroid treatment.[129]

Varicella-zoster virus-seropositive patients should receive prophylaxis with acyclovir or valacyclovir during the first year after HCT or until six months after discontinuation of immunosuppressive medications. A standard dose of acyclovir is 800 mg twice daily,[130] but some studies showed that 200 mg once daily was effective in preventing VZV reactivation.[131] Acyclovir should be started empirically if the patient presents with an acute abdomen or hepatitis typical of fulminant visceral VZV infection.[132] CMV monitoring in blood is continued beyond 100 days after HCT until one year for patients at risk of late CMV disease, including CMV-seropositive patients receiving high-dose corticosteroids, those who have already experienced CMV reactivation, and cord blood transplantation.[133] Pre-emptive therapy is usually considered for CMV levels of 250 IU/mL or more (equivalent to ≥1000 copies/mL) or a positive antigenemia test.

Community-acquired respiratory virus infections are an important cause of morbidity and mortality after HCT. The most frequent viruses include rhinovirus, respiratory syncytial virus (RSV), parainfluenza viruses (PIV), human metapneumovirus, and influenza viruses as these frequently cause lower respiratory tract disease associated with 12%-100% mortality.[134] An immunodeficiency scoring index can predict severity of RSV infection.[135] Aerosolized ribavirin showed efficacy in treating lower tract RSV after HCT.[136]

Combination therapy with immunomodulators such as intravenous immunoglobulin or palivizumab has been seen to have variable success.[137] Treatment for PIV infection has not been established. Efficacy of ribavirin has been limited for patients with lower respiratory tract infection of PIV.[138] Novel drugs such as a recombinant sialidase fusion protein and a hemagglutinin-neuraminidase inhibitor are under investigation.[138]

Solid cancers

There is an increased risk of solid cancers following both autologous and allogeneic HCT compared with the general population. The cumulative incidence is 1%-6% at ten years after HCT, and continues to rise over time without a plateau.[139-142] The most common sites include oral cavity, skin, breast and thyroid, but rates are also elevated in esophagus, liver, nervous system, bone and connective tissues compared with the general population.[143] Myeloablative TBI, young age at HCT, chronic GvHD and prolonged immunosuppressive medications beyond two years are well-documented risk factors for many types of cancers.[143] All HCT recipients should be advised of the risk of second cancers and should be encouraged to undergo recommended screening tests based on their predisposition.[143] The 5-year overall survival rates after diagnosis of solid cancers varied by cancer site, with 88%-100% for thyroid, testis and melanoma, approximately 50% for breast, mouth, soft tissue and female reproductive organs, and 20% or less for bone, lower gastrointestinal tract, and central nervous system.[144] These rates were similar to those of *de novo* cancers, except that rates were lower for female reproductive organs, bone, colorectum, and central nervous system, although further studies are warranted to confirm this observation. There is emerging evidence that human papilloma virus (HPV) is involved in the pathogenesis of squamous cell cancer after HCT.[145,146] The efficacy of HPV vaccination in preventing squamous cell cancer after HCT remains to be determined in prospective studies.[147]

Neuropsychological effects

Neuropsychological effects after HCT are being increasingly recognized and include, among others, depression, post-traumatic stress disorder, and neurocognitive deficits. Depression occurs in 12%-30% of HCT survivors and is more frequent in female patients, younger patients and those with poor social support, history of recurrent disease, chronic pain, and chronic GvHD.[148] Post-traumatic stress disorder occurs in 28% of patients at six months after HCT and may persist for 5%-13% of cases, although its risk factors are not yet clear.[148-150]

Neurocognitive deficits, so called "chemo brain", have

Table 1. Late effects after blood and marrow transplantation

Late effect	Incidence	Mortality	Morbidity	Treatable	Preventable
Cardiovascular	+	+	+	+	+
Pulmonary					
Bronchiolitis obliterans syndrome	+	++	++	+	-
Cryptogenic organizing pneumonia	+	+	+	++	-
Pulmonary hypertension	+	++	++	+	-
Endocrine					
Thyroid dysfunction	++	-	-/+	+++	-
Diabetes	++	+	+	+++	-
Dyslipidemia	++	-	-/+	+++	-
Adrenal insufficiency	+	-	-/+	+++	-/+
Gonadal dysfunction/ infertility	+++	-	-	-/+	-/+
Iron overload	++	-	-	++	-
Liver					
Hepatitis B	+	-	+	++	+
Hepatitis C and cirrhosis	+	-	+	++	-/+
Nodular regenerative hyperplasia	+	-	-	-	-
Focal nodular hyperplasia	+	-	-	-	-
Kidney					
Thrombotic microangiopathy	+	+	++	-/+	-
Nephrotic syndrome	+	-	++	++	-
Idiopathic chronic kidney disease	+	-	++	+	-
Bone					
Osteoporosis/osteopenia	++	-	-	++	+
Avascular necrosis	+	-	++	++	-
Infection	++	+	+	+++	+
Solid cancer	+	++	+++	-/+	-
Neuropsychological	++	-	++	+	-
Recurrent disease	++	+++	+++	-/+	-
Chronic graft-*versus*-host disease	++	+	++	+	-

+ : <20%; ++ : 20%-50%; +++ : >50%.

Table 2. Tests, preventive approaches and treatment of late effects.

Late effect	Tests	Preventive approaches	Treatment
Cardiovascular			
Anthracycline-related cardiomyopathy	Physical exam, chest X-ray, electrocardiogram, echocardiogram, brain natriuretic peptide level	Dexrazoxane, ACE inhibitors, ARBs, beta-blockers	ACE inhibitors, ARBs, beta-blockers
Others	Blood pressure, lipid panel, glucose level, HbA1c, glycoalbumin	Lifestyle modification, ACE inhibitors, ARBs	
Pulmonary			
Bronchiolitis obliterans syndrome	%FEV1, FEV1/FVC	Prednisone, FAM	
Cryptogenic organizing pneumonia	CT, lung biopsy	Prednisone, macrolides	
Pulmonary hypertension	High-resolution chest CT, echocardiography, cardiac catheterization		Oxygen, phosphodiesterase-5 inhibitors, inhaled nitric oxide, diuretics, bipyridine inotropes, after-load reducing agents
Endocrine			
Hypothyroidism	Thyroid-stimulating hormone, thyroxine levels		Replacement therapy
Diabetes	Glucose level, HbA1c, glycoalbumin		Lifestyle modification, hyperglycemic agents, insulin
Dyslipidemia	Lipid panel		Lifestyle modification, statins, fibrates, fish oil (omega-3 fatty acids), ezetimibe
Adrenal insufficiency	Cortisol-stimulation test	Alternate-day regimen when corticosteroids are used	Hydrocortisone, low-dose prednisone
Gonadal dysfunction			
Male patients	Testosterone level		Testosterone replacement
Female patients	Follicle-stimulating hormone, lutenizing hormone, estradiol levels	Reduced-intensity conditioning	Hormone replacement
Infertility	Sperm test	Semen banking, cryopreservation of testicular or ovarian tissues	Assisted reproduction, surrogate pregnancy, adoption
Iron overload	Serum ferritin levels, transferrin saturation, Prussian blue-stained marrow biopsy, T2* MRI, FerriScan, SQUID		Phlebotomy, desferoxamine, deferasirox
Liver			
Hepatitis B	ALT, HBV DNA levels	Entecavir, lamivudine	Entecavir, lamivudine
Hepatitis C and cirrhosis	ALT, HCV RNA levels	Direct acting antiviral agents	Direct acting antiviral agents, interferon

continued in the next page

adverse functional impacts on HCT survivors who return to work and daily activities that require short-term memory, information-processing speed, multitasking and co-ordination.[151] Neuropsychological tests can help identify neurocognitive deficits. Most evidence is derived from studies of breast cancer survivors, with estimated rates of deficits ranging from 16% to 50% up to ten years after treatment.[152,153] Potential mechanisms for chemotherapy-induced neurocognitive changes include cytokine and immune dysregulation, damage to DNA and telomere length through cytotoxic agents, oxidative stress and hormonal changes.[154] In cases of HCT survivors, there may be additional deficits derived from neurological complications including nervous system infection (HHV-6, fungi, etc.), immune-mediated damage, and toxicities of calcineurin inhibitors such as TMA and posterior reversible encephalopathy syndrome. A prospective observational study showed that neurocognitive function declined substantially at 80 days after HCT, returned to pre-transplantation levels at one year, and continued to improve between one and five years after HCT, except for motor dexterity and verbal learning and retention.[155] Mostly mild, neurocognitive dysfunction according to the Global Deficit Score persisted at five years in 42% of long-term survivors.[155] Rehabilitation programs have succeeded in improving neurocognitive functions,[156] and methylphenidate and modafinil have demonstrated variable efficacies to improve neurocognitive function in non-HCT cancer patients.[157,158] Efficacies of these interventions remaine to be determined among HCT survivors.

Influence of newer practices on late effects

An understanding of the influence of newer practices such as cord blood transplantation, non-TBI or reduced-intensity conditioning regimens and older patients on the incidence and severity of late effects awaits longer follow up. For example, TBI is associated with an increased risk of many late effects such as cardiovascular diseases, COP, hypothyroidism, diabetes, dyslipidemia, infertility, TMA-related kidney injury, bone density loss, avascular necrosis, and secondary solid cancer.[49,54,100,102,114,118,143,159,160] The use of non-TBI conditioning regimens might reduce the burden of these late effects among HCT survivors. Some studies found that cumulative incidences of late effects did not differ much after reduced-intensity regimens compared with myeloablative regimens,[15,161] and reduced-intensity conditioning was associated with a higher risk of recurrent malig-

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Late effect	Tests	Preventive approaches	Treatment
Kidney			
Thrombotic microangiopathy	CBC, schistocytes, serum creatinine, lactate dehydrogenase, haptoglobin, renal biopsy		Taper or stop calcineurin inhibitors, GvHD treatment required in some cases
Nephrotic syndrome	Urine protein, renal biopsy		Prednisone, rituximab, mycophenolate mofetil,
Idiopathic chronic kidney disease	Renal biopsy		ACE inhibitors, ARBs
Bone			
Osteoporosis/osteopenia	Dual-energy X-ray absorptiometry	Calcium intake, vitamin D intake, bisphosphonate, estrogen, testosterone	Bisphosphonate, estrogen, testosterone, (calcitonin, raloxifene, denusomab, romosozumab, blosozumab)
Avascular necrosis	MRI		Conservative treatment, surgery
Infection			
Pneumocystis jirovecii	Bronchoalveolar lavage, PCR, β-D-glucan	Trimethoprim-sulfamethoxazole, dapsone, atovaquone	Prednisone, trimethoprim-sulfamethoxazole, atovaquone, pentamidine
Encapsulated bacteria		Trimethoprim-sulfamethoxazole, penicillin, azithromycin, vaccination against *Haemophilus influenzae type b, Neisseria meningitidis, Streptococcus pneumoniae*	Antibiotics
Fungi	Galactomannan assay, β-D-glucan, CT	Posaconazole, voriconazole	Antifungal agents
Varicella-zoster virus	PCR	Acyclovir, valacyclovir	Acyclovir, valacyclovir
Cytomegalovirus	PCR, antigenemia	Ganciclovir, valganciclovir, foscarnet	Ganciclovir, valganciclovir, foscarnet
Respiratory syncytial virus	PCR	Aerosolized ribavirin, palivizumab	
Influenza virus	Immunoassay	Vaccination	Oseltamivir
Solid cancer	Recommended screening tests (see reference [143])	(Human papillomavirus vaccination)	Site- and stage-specific treatment
Neuropsychological	Neuropsychological test, MRI		Rehabilitation, methylphenidate, modafinil

ACE: angiotension-converting enzyme; ARBs: angiotensin II receptor blockers; FAM: inhaled fluticasone propionate, azithromycin and montelukast; CT: computed tomography; MRI: magnetic resonance imaging; SQUID: superconducting quantum interference device; ALT: alanine aminotransferase; GvHD: graft-*versus*-host disease; PCR: polymerase chain reaction.

nancy among patients with myeloid malignancy.[162] One study showed that the risk of AVN was elevated after cord blood transplantation, but graft source had a limited influence on other long-term health status and QOL.[163]

Consensus guidelines for late effects and prevention behaviors

Incidence, mortality, morbidity and management of individual late effects are summarized in Tables 1 and 2. Recognizing the importance of managing late effects after HCT, the Center for International Blood and Marrow Transplant Research (CIBMTR), the European Group for Blood and Marrow Transplantation (EBMT), and the American Society for Bone Marrow Transplantation (ASBMT) developed recommendations in 2006 for screening and prevention practices for HCT survivors.[164] Consensus recommendations were up-dated in 2011 including other international transplant communities.[21] The NIH convened working groups to formulate late effects initiatives in 2015.[148,165-169]

Despite higher levels of engagement with health care providers, HCT survivors had similar health and prevention behaviors as matched untransplanted controls, suggesting the need for further education of both HCT survivors and health practitioners.[170] Major modifiable predictors of lower adherence to preventive care practices were concerns about medical costs and lack of knowledge.[171]

Conclusion

While the number of HCT survivors is growing, there is no evidence that the burden of late effects is lessening. HCT survivors face myriad late effects that can limit their functioning, require prolonged or life-long medical treatment, reduce their quality of life and also shorten their survival. To the extent that the HCT procedure itself causes these late effects, the transplant community has a responsibility to appropriately monitor, treat and ultimately try to prevent late effects. Given the dispersion of survivors and the varied structure of health care, hematologists, oncologists, primary care physicians and medical subspecialists are all involved in providing this care. Further research is needed to understand the biology of late effects to help identify better prevention and treatment strategies.[166]

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