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REPORT

National Cancer Institute–National Heart, Lung and Blood Institute/Pediatric Blood and Marrow Transplant Consortium First International Consensus Conference on Late Effects After Pediatric Hematopoietic Cell Transplantation: Long-Term Organ Damage and Dysfunction

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Long-term complications after hematopoietic cell transplantation (HCT) have been studied in detail. Although virtually every organ system can be adversely affected after HCT, the underlying pathophysiology of these late effects remain incompletely understood. This article describes our current understanding of the pathophysiology of late effects involving the gastrointestinal, renal, cardiac, and pulmonary systems, and discusses post-HCT metabolic syndrome studies. Underlying diseases, pretransplantation exposures, transplantation conditioning regimens, graft-versus-host disease, and other treatments contribute to these problems. Because organ systems are interdependent, long-term complications with similar pathophysiologic mechanisms often involve multiple organ systems. Current data suggest that post-HCT organ complications result from cellular damage that leads to a cascade of complex events. The interplay between inflammatory processes and dysregulated cellular repair likely contributes to end-organ fibrosis and dysfunction. Although many long-term problems cannot be prevented, appropriate monitoring can enable detection and organ-preserving medical management at earlier stages. Current management strategies are aimed at minimizing symptoms and optimizing function. There remain significant gaps in our knowledge of the pathophysiology of therapy-related organ toxicities disease after HCT. These gaps can be addressed by closely examining disease biology and identifying those patients at greatest risk for adverse outcomes. In addition, strategies are needed for targeted disease prevention and health promotion efforts for individuals deemed at high risk because of their genetic makeup or specific exposure profile.

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INTRODUCTION

The incidence of and risk factors for long-term complications after hematopoietic cell transplantation (HCT) have been studied in detail. Virtually every organ system can be adversely affected in some way after HCT, and although much is known about these potential toxicities, the underlying pathophysiology of most are incompletely understood.

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In April 2011, a National Cancer Institute (NCI)- and National Heart, Lung and Blood Institute (NHLBI)-Pediatric Blood and Marrow Transplant Consortium (PBMTC)-sponsored consensus conference of international experts in clinical and biological research into late effects after HCT convened to review the state of the science of pediatric studies and identify key areas for future research. This article presents the conclusions shared at that conference relating to the pathophysiology of late effects involving the gastrointestinal (GI), renal, cardiac, metabolic, and pulmonary systems. Underlying diseases, pretransplantation exposures, transplantation conditioning regimens, graft-versus-host disease (GVHD), and other treatments all contribute to these problems. No organ system functions independently, and thus long-term complications are usually interrelated and only rarely limited to a single system.

Iron Overload

Secondary iron overload is a nearly universal complication of HCT. The most troublesome complications of iron overload are not hepatic-related, but rather cardiac-, pancreatic-, pituitary-, and thyroid-related. It develops from repeated red blood cell transfusions and increased GI iron absorption in the setting of ineffective erythropoiesis and inflammatory conditions, including GVHD [1]. Patients undergoing transplantation for chronic anemia or protracted hematologic malignancy may have a substantial iron burden [2,3]. Iron overload after transplantation for hematologic malignancy is very common, ranging from 1832 to 13,120 g/g dry weight (measured biochemically) before day 100 post-HCT [4]. The effects of iron overload on morbidity in transplantation survivors have not been fully investigated, although one study evaluated these effects in patients undergoing HCT for thalassemia [5].

Recent studies using serum ferritin as a marker suggest that iron levels fall slowly over time after transplantation, reaching normal levels only years later [6,7]. Humans cannot excrete excess iron; iron mobilization and removal is needed to accelerate this process, given that prolonged iron excess can lead to excessive morbidity [8]. Phlebotomy can mobilize iron from overloaded tissues if the patient has recovered normal erythropoiesis [9]. In a patient with heavy iron overload, iron reduction therapy may improve transplantation outcome [10] and cardiac function [5], but little data are available on transplantation survivors with underlying diseases other than thalassemia. Table 1 summarizes the literature addressing the adverse health outcomes from excessive body iron.

To date, application of iron-specific magnetic resonance imaging (MRI) to the study of transplantation survivors is lacking. Risk factor analysis of survivors with iron burden as a cofactor have not yet been carried out with regard to cardiac events, growth and development, gonadal development, fertility, endocrine dysfunction, fibrotic liver disease, and secondary malignancy. The threshold of cardiac iron concentration for cardiac events is unknown. The most important recent development has been standardization of the T*2-weighted MRI technique for quantifying tissue iron. This methodology will provide a foundation for future studies of transplantation survivors. Using T*2-weighted MRI, epidemiologic studies of various designs (prospective, cross-sectional, and disease-specific) are urgently needed to better understand the role of iron overload on long-term transplantation outcomes. Intervention studies should then follow.

Table 1. Potential Clinical Consequences of Iron Overload in HCT Survivors, Based on Data from Studies of Iron Burden in Nontransplantation Populations

Organ Involved	Potential Consequences	References
Heart	Cardiac failure, arrhythmias, death	[1-13]
Pituitary	Hypogonadism, delayed puberty, growth hormone deficiency	[14-16]
Thyroid	Hypothyroidism	[14,15]
Pancreas	Insulin-dependent diabetes mellitus	[14,17-20]
Brain	Neurocognitive defects	[21,22]
Secondary malignancy	Solid tumor development	[23-26]

GI, Hepatobiliary, and Pancreatic Dysfunction

Gut symptoms in the years after HCT are usually a continuation of problems occurring during the first year (eg, protracted acute GVHD, chronic GVHD, medication side effects, infection related to immune suppression). The frequency and severity of these problems wanes with time, but new problems involving the gut and liver may arise decades later. Table 2 lists symptoms and causes of GI problems associated with HCT.

The majority of GI late effects are GVHD-related. Unfortunately, the significant current knowledge gaps include the mystery of why some patients fail to develop graft tolerance and why others suffer from refractory chronic GVHD. Current research on GVHD biomarkers may help identify flares, enabling preemptive therapy. Areas of future focus should include acceleration of immune reconstitution, development of tolerance, and discovery of markers of incipient GVHD. New therapies for protracted acute and chronic GVHD are urgently needed.

Chronic Kidney Disease

Chronic kidney disease (CKD) is frequently diagnosed after HCT. Of the multiple clinical forms of CKD, the most commonly described are thrombotic microangiopathy, nephrotic syndrome, calcineurin inhibitor toxicity, acute kidney injury, and GVHD-related CKD. Various risk factors associated with the development of CKD have been described; however, some recent studies have suggested that GVHD also may be a proximal cause of renal injury, as discussed later.

Table 2. Causes of GI, Hepatobiliary, and Pancreatic Problems in Long-Term HCT Survivors

Problem Areas	Common Causes	Less Common Causes
Esophageal symptoms [27-32] • Heartburn • Dysphagia • Painful swallowing	• Oral chronic GVHD (mucosal changes, poor dentition, xerostomia) • Reflux of gastric fluid	• Chronic GVHD of the esophagus (webs, rings, submucosal fibrosis, and strictures, aperistalsis) • Hypopharnngeal dysmotility (myasthenia gravis, cricopharyngeal incoordination) • Squamous > adenocarcinoma • Pill esophagitis • Infection (fungal, viral)
Upper gut symptoms: anorexia, nausea, vomiting [33-37]	• Protracted acute GI GVHD • Activation of latent infection (CMV, HSV, VZV) • Medication adverse effects	• Secondary adrenal insufficiency • Acquisition of infection (enteric viruses, giardia, cryptosporidia, *Haemophilus pylori*) • Gut dysmotility
Mid-gut and colonic symptoms: diarrhea and abdominal pain [38,39]	• Protracted acute GI GVHD • Activation of latent CMV, VZV • Drugs (eg, mycophenolate mofetil, Mg^{++}, antibiotics)	• Acquisition of infection (enteric viruses, bacteria, parasites) • Pancreatic insufficiency • Clostridium difficile colitis • Collagen-encased bowel (GVHD) • Rare: inflammatory bowel disease, sprue [39]; bile salt malabsorption; disaccharide malabsorption
Liver problems [40-50]	• Cholestatic GVHD • Chronic viral hepatitis (B and C) • Cirrhosis • Focal nodular hyperplasia • Nonspecific elevation of liver enzymes in serum (AP, ALT, GGT)	• Hepatitic GVHD • VZV or HSV hepatitis • Fungal abscess • Nodular regenerative hyperplasia (NRH) • Biliary obstruction • Drug-induced liver injury
Biliary and pancreatic problems [51-54]	• Cholecystitis • Common duct stones/sludge • Gall bladder sludge (calcium bilirubinate) • Gallstones	• Pancreatic atrophy/insufficiency • Pancreatitis/edema, stone- or sludge-related • Pancreatitis, tacrolimus-related

AP indicates alkaline phosphatase; ALT, alanine transaminase; CMV, cytomegalovirus; GGT, gamma glutamyl transpeptidase; HSV, herpes simplex virus; VZV, varicella zoster virus.

A systematic review of 9317 adults and children who underwent HCT from 28 study cohorts found that approximately 16.6% (range, 3.6%-89%) of patients developed CKD, defined as a decrease in estimated glomerular filtration rate of at least 24.5 mL/min/1.73 m^2 within the first year after HCT [55]. The cumulative incidence of CKD developing approximately 5 years after HCT ranges from 4.4% to 44.3%, depending on the type of transplant and stage of CKD [56,57]. In this setting, mortality is significantly higher in transplant recipients with CKD than in recipients who retain normal renal function, even when controlling for comorbidities [58]. Patients who develop CKD after HCT have a range of possible outcomes, including end-stage renal disease requiring chronic dialysis and renal transplantation.

The mechanisms of HCT-related chronic renal dysfunction remain unknown. Although many clinical factors have been associated with the development of CKD, findings from the Seattle group and others have refuted previous traditional risk factors, such as total body irradiation (TBI)-containing conditioning regimens [59-61]. These new data suggest that acute and chronic GVHD are the primary pathogenic mechanisms. Early studies focused on patients receiving TBI as part of a conditioning regimen who later developed hemolytic uremic syndrome [62-67], or on patients who developed nephrotic syndrome after HCT [68]; however, these specific subtypes of renal disease likely do not account for the majority of cases of CKD. Current thinking regarding the pathophysiology of CKD implicates GVHD and/or the therapies used to manage GVHD (Figure 1).

This new paradigm positing HCT-related CKD as a renal manifestation of GVHD involves 2 possible mechanisms: The kidney could be a direct target of T cell–mediated renal damage, or the chronic systemic inflammatory state of GVHD could lead secondarily to cytokine-mediated nephropathy. A third potential

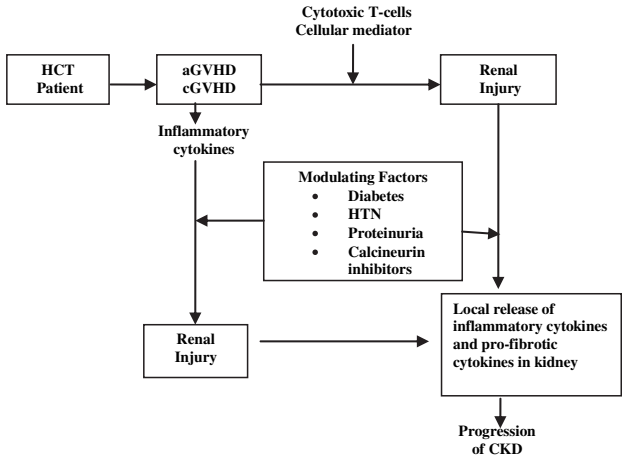

Figure 1. Proposed conceptual representation of pathogenesis of CKD in HCT recipients. aGVHD, acute GVHD; cGVHD, chronic GVHD; HTN, hypertension.From Hingorani S. Kidney and bladder complications of hematopoietic cell transplantation. In: Thomas ED, Appelbaum FR, Forman SG, et al., editors. *Hematopoietic Cell Transplantation*. 4th ed. Hoboken, NJ: Wiley-Blackwell; 2009. p. 1473.

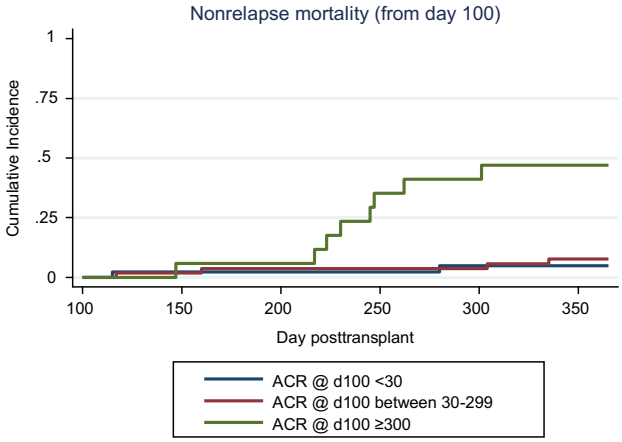

Figure 2. Cumulative incidence curves of albuminuria and nonrelapse mortality from day 100 to 1 year post-HCT: n = 43 for albumin/creatinine ratio (ACR) <30; n = 54 for ACR 30-299; n = 17 for ACR ≥300. Hingorani SR, Seidel K, Lindner A, Aneja T, Schoch G, McDonald G. Albuminuria in hematopoietic cell transplantation patients: prevalence, clinical associations, and impact on survival. *Biol Blood Marrow Transplant.* 2008 Dec;14(12):1365-72.

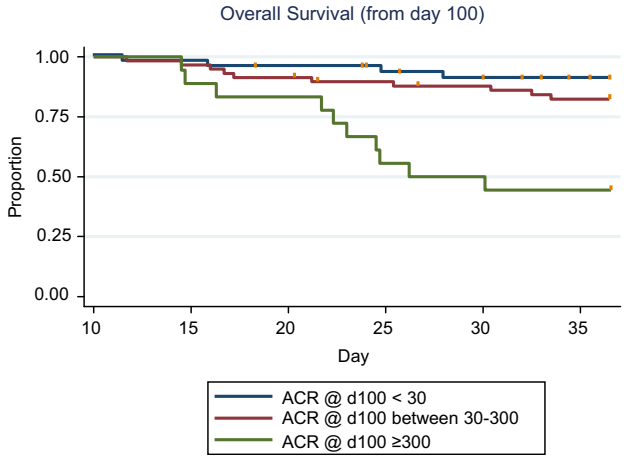

Figure 3. Kaplan-Meier curves of albuminuria and overall survival from day 100 to 1 year post-HCT: n = 44 for albumin/creatinine ratio (ACR) <30; n = 58 for ACR 30-299; n = 18 for ACR ≥300. Hingorani SR, Seidel K, Lindner A, Aneja T, Schoch G, McDonald G. Albuminuria in hematopoietic cell transplantation patients: prevalence, clinical associations, and impact on survival. *Biol Blood Marrow Transplant.* 2008 Dec;14(12):1365-72.

explanation is that chronic exposure to calcineurin inhibitors, such as cyclosporine and tacrolimus used for GVHD prevention and/or treatment, causes CKD. These are not necessarily mutually exclusive hypotheses, given that T cell–mediated injury in GVHD is intertwined with the effects of cytokines [69], and that the effects of cyclosporine can be potentiated in the presence of a chronic inflammatory state. In an autopsy study of 26 patients undergoing autologous and allogeneic transplantations, renal tubulitis identical to that seen in renal allograft rejection was found in 67% of the patients [70]. In a report of minimal change nephrotic syndrome that developed after HCT, large numbers of $CD8^+$ donor T cells were found infiltrating the interstitium and periglomerular areas of the kidney [71]. A mouse model of GVHD kidney disease has shown that progressive venulitis, endothelialitis, and tubulitis can begin within 2 weeks after HCT [72].

Although albuminuria and other conventional risk factors for progressive renal disease have been identified in other patient populations, little is known about risk factors for CKD progression or why CKD and proteinuria increase nonrelapse mortality in the HCT patient population. In a cohort of 142 patients (median age, 47 years) undergoing first HCT, albuminuria and proteinuria at day 100 post-HCT were associated with an increased risk of CKD, nonrelapse mortality (hazard ratio, 12.8; 95% confidence interval, 2.7-60.6), and overall mortality (hazard ratio, 7.7; 95%, confidence interval, 2.4-24.7) at 1 year post-HCT (Figures 2 and 3) [73]. In a cohort of 376 patients with CKD at 1 year post-HCT (defined as glomerular filtration rate <60 mL/min/1.73 m^2), 8% of the 109 patients for whom follow-up data was available (up to 8 years) progressed to end-stage renal disease.

Albuminuria and proteinuria may reflect GVHD-induced endothelial injury, inflammatory tubular and interstitial damage, and progressive CKD; however, whether albuminuria and proteinuria by themselves cause the increased morbidity and mortality of HCT, or merely reflect other processes, is unclear. Recent research has focused on the direct role of albuminuria and proteinuria on progression of CKD [74]. It is thought that albuminuria triggers the release of proinflammatory cytokines and chemokines that recruit macrophages and other inflammatory cells into the interstitium, causing fibrosis and progression of CKD. It may be that in patients undergoing HCT, inflammatory damage to the tubules from GVHD leads to albuminuria, which is a manifestation of renal GVHD. Establishing such a mechanism would have important therapeutic implications. Thus, determining whether albuminuria and proteinuria are epiphenomena or true independent risk factors for progression and mortality in the HCT population is critical before changes in management can be proposed in a prospective clinical trial. Longer-term follow-up is needed in these patients to determine whether progression occurs from albuminuria to overt proteinuria and then to end-stage renal disease or whether these conditions resolve with successful treatment of GVHD and associated inflammation.

Extrapolating from previous studies in patients with diabetes, we speculate that ace inhibitors and angiotensin II receptor blockers would be useful in patients with albuminuria and hypertension after HCT. In fact, Cohen et al. [75] led a single-institution trial in which patients were randomized to receive either captopril (n = 28) or placebo (n = 27) starting on day +35 after HCT. The patients who received

placebo had a 15% incidence of hemolytic uremic syndrome at 1 year, compared with a 4% incidence in treated patients. Five-year survival was 20% in the placebo group and 45% in the captopril group.

Current evidence suggests the need to think differently about CKD in patients after HCT. Most post-HCT CKD is not secondary to TBI or cyclosporine use,. but rather may be a consequence of nephropathic processes such as GVHD and the accompanying chronic inflammatory state (Figure 1). Clearly, we first need to better define the scope of the problem of CKD in this patient population using accurate and sensitive measures of kidney function. Identifying those patients at risk for the development of CKD will be important for early intervention and even prevention clinical trials in this patient population. To determine how to best minimize and treat CKD, future studies will need to focus on the mechanisms through which GVHD leads to renal injury, determining whether albuminuria is an indicator of disease or a target for therapy, optimizing prevention strategies, and identifying how best to measure posttransplantation renal function.

Cardiovascular Disease

Cardiovascular (CV) complications are a leading cause of therapy-related morbidity and mortality in long-term survivors of childhood malignancy [76-79]. A strong dose-dependent association between anthracycline exposure and the risk of congestive heart failure (CHF) is well recognized in patients not undergoing HCT; the risk is modified by younger age at exposure, female sex, and chest irradiation [80-83]. Less is known regarding the incidence and predictors of CHF after HCT in childhood. Potentially cardiotoxic exposures unique to HCT include conditioning with high-dose chemotherapy (especially cyclophosphamide) and TBI [83]. In addition, HCT survivors are at increased risk of developing such CV risk factors as hypertension and diabetes, due in part to exposure to TBI, prolonged immunosuppressive therapy after allogeneic HCT, and other health conditions, such as hypothyroidism or growth hormone deficiency [83,84]. The modifying influence of these CV risk factors on the risk of CHF after cardiotoxic therapy has not been fully investigated.

The independent roles of pre-HCT exposure to therapeutic agents, transplantation-related conditioning, and comorbidities in the development of late CHF after HCT have been examined recently [85]. Patients with late CHF were identified from a cohort of nearly 3000 1+-year survivors of HCT. Pre-HCT exposure to anthracyclines and the presence of post-HCT comorbidities were the primary risk factors for late CHF after HCT. Conditioning-related exposures did not appear to contribute significantly to this risk. The cardiotoxic effect of anthracyclines was greatest in recipients of autologous HCT, with a cumulative dose of $\geq$250 mg/m^2 associated with a 30-fold increased risk of late CHF. Overall survival was <50% at 2 years after diagnosis of CHF. A subsequent study evaluating long-term health-related outcomes in 3 cohorts—conventionally treated childhood cancer survivors, survivors of childhood HCT, and sibling controls—found that although HCT survivors had a 13-fold greater risk of severe or life-threatening CV complications compared with healthy controls, the risk was equivalent to that seen in conventionally treated patients [86]. One possible explanation for this finding is that, as reported previously [85,87], the risk for late-occurring CV complications after HCT may be due largely to pre-HCT therapeutic exposures, with little additional risk from conditioning-related exposures or GVHD.

It is becoming increasingly recognized that risks for many diseases result from an interaction between inherited gene variants and environmental factors, including chemical, physical, and behavioral factors. However, large gaps remain in our knowledge of the pathogenesis of therapy-related adverse events. Emerging evidence suggests that individual genetic susceptibility might be a determinant of therapy-related CHF [88,89]. Significant cardiotoxicity has been reported at cumulative doses of <250 mg/m^2 [9], whereas doses exceeding 1000 mg/m^2 have been tolerated without long-term sequelae by a few individuals [90]. In one study of long-term HCT survivors, 40% of the patients with clinical CHF received a cumulative dose of <250 mg/m^2 [11]. This heterogeneity might be explained, at least in part, by the presence of genetic polymorphisms that alter the metabolism of anthracyclines, the myocardial response to the drug, as well as other factors thought to play a role in susceptibility to de novo disease [88,89,91].

A recent case-control study examined the role of functional single nucleotide polymorphisms in genes involved in free radical metabolism (NAD[P]H oxidase: subunits *NCF4*, *RAC2*, and *CYBA*) as well as those affecting the synthesis of cardiotoxic anthracycline alcohol metabolites (carbonyl reductase: *CBR1* and *CBR3*) in modifying the risk of CHF after HCT [92]. Patients with CHF and controls without CHF were matched by age at HCT, type of HCT, ethnicity, anthracycline dose, and duration of follow-up. Multivariate conditional logistic regression revealed that a polymorphism in the NAD(P)H oxidase subunit *RAC2* (rs13058338, 7508T→A) conferred a 3.2-fold greater risk of anthracycline-related CHF (odds ratio [OR], 3.2; P = .05), and that the GG genotype of rs9024 (1096G→A) in *CBR1* carried a 10.8-fold greater risk (OR, 10.8; P = .04). These preliminary findings support the "unifying hypothesis" [93] that anthracycline-related CHF can develop as a result of oxidative stress or metabolic derangements induced by cardiotoxic alcohol metabolites, and that the

high-risk variants of *RAC2* and *CBR1* play critical roles in modifying this risk. Replication and confirmation of these findings by others in independent study samples could set the stage for identifying a subgroup of patients up front who could perhaps receive alternative treatment for management of cancer; whereas for those who have already received anthracyclines, identification of high-risk alleles would warrant closer surveillance for cardiotoxicity and use of medications that modulate cardiac function.

Insulin Resistance and Abnormal Body Composition

Survivors of allogeneic HCT have a 2.3-fold greater risk for premature CV-related death compared with the general population [94,95]. The exact etiology of CV risk and subsequent death is largely unknown, although the development of "metabolic syndrome" (the constellation of central obesity, insulin resistance, glucose intolerance, dyslipidemia, and hypertension associated with a substantially increased risk for type 2 diabetes mellitus and atherosclerotic CV disease [Table 3]) and, more specifically, insulin resistance as a consequence of HCT have been suggested [96-98]. Studies comparing conventionally treated leukemia survivors and HCT survivors found that the HCT survivors were significantly more likely to manifest metabolic syndrome and multiple adverse cardiac risk factors, including central adiposity, hypertension, insulin resistance, and dyslipidemia [99-100]. The concern is that over time, survivors who develop metabolic syndrome after HCT will be at greater risk for developing significant CV-related events and/or premature death from CV-related causes. The Bone Marrow Transplant Survivor Study examined diabetes, hypertension, and cardiovascular events in 1089 patients surviving 2 years or longer after HCT [100]. At a mean age of 39 years and with a mean post-HCT follow-up of nearly 9 years, survivors of allogeneic HCT were 3.6 times more likely to report diabetes than siblings and twice as likely to report hypertension. TBI exposure also was associated with an increased risk of diabetes (OR, 3.42; 95% CI, 1.55-7.52). CV outcomes were also examined in nearly 1500 >2-year HCT survivors treated in Seattle between 1985 and 2006 relative to an age-, year-, and sex-matched population-based comparison group [101]. Using state hospital and death registry data defining key CV outcomes revealed that the HCT survivors had a higher rate of CV-related mortality and a greater cumulative incidence of ischemic heart disease, cardiomyopathy/heart failure, stroke, vascular diseases, and rhythm disorders. The survivors also had a greater cumulative incidence of related conditions that predispose to more serious cardiovascular disease, including hypertension, renal disease, dyslipidemia, and diabetes.

Table 3. Adult Treatment Panel III Criteria for Metabolic Syndrome: Indicated by 3 or More Positive Findings

Criterion	Adults	Adolescents*
High triglyceride level, mg/dL	≥150	≥110
Low high-density lipoprotein cholesterol level, mg/dL		
Males	<40	≤40
Females	<50	≤40
Abdominal obesity, waist circumference, cm		
Males	>102	≥90th percentile
Females	>88	≥90th percentile
High fasting glucose level, mg/dL	≥100†	≥100†
High blood pressure, mm Hg	≥130/85	≥90th percentile

*Adult Treatment Panel III criteria modification for adolescents (age 12-19 years) as described by Cook et al. [105].
†The American Diabetes Association's 2003 definition lowered abnormal fasting glucose level to 100 mg/dL [106], and this change has been incorporated into the current definition of metabolic syndrome [107].

Why HCT survivors are at greater risk for adverse CV outcomes is not completely clear. Although descriptive and epidemiologic-based studies have at least called attention to the problem, thus far they have provided little insight into the underlying pathophysiology of CV disease in HCT survivors or clues as to why these events are more common in HCT survivors than the general population. We also know little, if anything, about whether any preventive strategies or other interventions might modify this risk.

The association of obesity with diabetes and risk of CV disease in the general population is well established, but obesity as determined by body mass index (BMI) is uncommon in long-term survivors of HCT [100]. However, even with a normal BMI, HCT survivors can develop significantly altered body composition, with an increase in total percent fat mass (PFM) and a decrease in lean body mass (LBM). This phenomenon, termed "sarcopenic obesity," results in a loss of myocyte insulin receptors and an increase in adipocyte insulin receptors (which are less efficient in binding insulin and clearing glucose), ultimately contributing to insulin resistance [101-103]. Preliminary data from 119 children and young adults (current mean age, 26.1 ± 0.8 years; 61.3% male) who had undergone HCT at a mean age of 12.2 ± 0.6 years and 81 healthy sibling controls (current mean age, 22.8 ± 0.9 years; 49.4% male) found that the HCT survivors had significantly lower weight, but the 2 groups had no differences in BMI or waist circumference [104]. HCT survivors had significantly higher PFM and lower LBM. Insulin resistance was measured by euglycemic hyperinslulinemic clamp studies, and results were adjusted for PFM. Compared with controls, HCT survivors were significantly more insulin-resistant hand had significantly higher levels of total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Interestingly, these differences were found only in patients who had received TBI as part of a transplantation conditioning regimen. These

preliminary data thus reveal that even at a relatively young age, HCT survivors have increased CV risk factors that are independent of obesity, but may be related to altered body composition (ie, decreased LBM and increased PFM), insulin resistance, and TBI exposure.

Although it is becoming more evident that HCT survivors are at increased risk for developing insulin resistance, the related mechanistic pathways and risk factors are still undefined, and identifying these at cellular and genetic levels will be critical. In addition, further definition of the role of altered body composition in insulin resistance and CV risk in HCT survivors is needed. Whether CV risk and abnormal body composition are related primarily to TBI exposure, corticosteroid exposure, a chronic inflammatory state (mediated or related to GVHD), or some other mechanism needs to be carefully examined. Finally, studies of the post-HCT time course of development of CV risk factors and changes in body composition are needed to will guide the development of preventive strategies and interventions.

Chronic Pulmonary Dysfunction

Declining lung function is a significant complication in the months and years after successful allogeneic HCT. Two forms of chronic pulmonary dysfunction are commonly observed: obstructive lung disease (OLD) and restrictive lung disease (RLD) [108-112]. The incidence of both forms can range from 10% to 40% depending on donor source, the time interval after HCT, definition applied, and presence of chronic GVHD [108]. In each scenario, collagen deposition and the development of fibrosis in the interstitial spaces (RLD) or the peribronchiolar spaces (OLD) are believed to contribute to the patterns of lung dysfunction detected on pulmonary function tests [113].

The most common form of OLD after allogeneic HCT is bronchiolitis obliterans (BO) [110, 114,115]. First reported in the 1980s, BO is a serious and potentially life-threatening late effect characterized by an inflammatory process resulting in bronchiolar obliteration, fibrosis, and progressive OLD [108]. Historically, BO has been used to describe chronic GVHD of the lung starting 6-20 months after HCT. Patients with BO may be initially asymptomatic but typically present with cough, wheezing, or dyspnea on exertion [113]. Pulmonary function testing reveals OLD with general preservation of forced vital capacity (FVC), reductions in forced expiratory volume in 1 second (FEV_1), and associated decreases in the FEV_1/FVC ratio with or without a significant decline in diffusion capacity of the lung for CO [35]. The diagnosis of OLD without histological confirmation is commonly termed BO syndrome (BOS). More recently, air flow obstruction has been defined as a >5% per year decline in percent predicted FEV_1 with the lowest posttransplantation FEV_1/FVC ratio <0.8 [116]. Risk factors for BO include lower pretransplantation FEV_1/FVC values, concomitant pulmonary infection, chronic aspiration, acute or chronic GVHD, older recipient age, use of a mismatched donor, and high-dose (versus reduced-intensity) conditioning [108,114]. The clinical course of BO is variable, but patients frequently develop progressive and debilitating respiratory failure despite the enhanced immunosuppression [108].

RLD is defined by reductions in FVC, total lung capacity (TLC), and diffusion capacity of the lung for CO. In contrast to OLD, the FEV_1/FVC ratio is maintained near 100%. RLD is common after HCT, reported in as many as 25%-45% of patients by day 100 [108]. Importantly, declines in TLC or FVC occurring at 100 days and 1 year post-HCT are associated with increased nonrelapse mortality. Early reports suggested that the incidence of RLD increases with advancing recipient age, but more recent studies have revealed significant RLD in children receiving HCT [117]. The most recognizable form of RLD is bronchiolitis obliterans organizing pneumonia (BOOP). Clinical features include dry cough, shortness of breath and fever. Radiographic findings include diffuse, peripheral, fluffy infiltrates consistent with airspace consolidation. Although reported in less than 10% of HCT recipients, the development of BOOP is strongly associated with previous acute and chronic GVHD [118].

The complex pathophysiology of chronic lung injury after HCT is poorly understood and represents the most significant gap in the current knowledge of this spectrum of late effects. This limitation stems from the paucity of (1) correlative data obtained from afflicted HCT recipients, (2) controlled clinical trials, and (3) suitable animal models for either RLD or OLD. RLD and OLD after HCT likely involve an initial insult to the pulmonary vascular endothelium and leukocyte recruitment into the lung parenchyma, followed by a dysregulated reparative response characterized by the interplay among recruited donor-derived leukocytes, bronchiolar and interstitial epithelial cells, and lung fibroblasts and the ultimate deposition of collagen [108]. The possible role of innate immunity in the development of OLD was recently highlighted by 2 clinical studies. Investigators found that genetic variations in the bactericidal/permeability-increasing protein and nucleotide-binding oligomerization domain containing caspase-2 recruitment domain family member 15 (NOD2/CARD15) influence the risk of airflow obstruction and BO after allogeneic HCT [119,120].

A triphasic model of RLD and OLD after HCT has been proposed in which alloantigen recognition is the inciting stimulus for pulmonary inflammation [108]. In phase I, an acute pneumonitis develops as a consequence of an alloimmune response, resulting

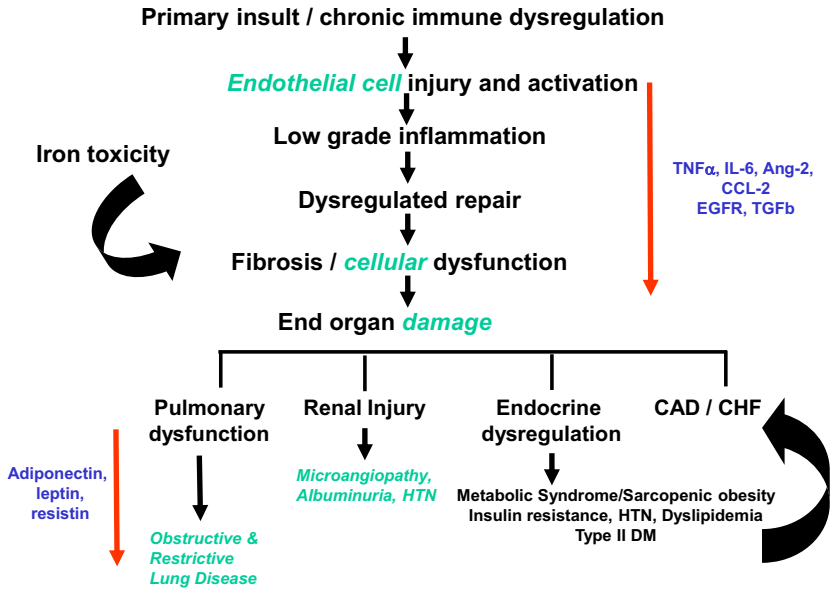

Figure 4. Mechanisms of cellular damage and organ response.

in the sequential influx of lymphocytes, macrophages, and neutrophils into an inflamed lung parenchyma. In phase II, the persistence of an inflammatory signal in the setting of exuberant repair mechanisms promotes the transition from acute to chronic injury. If the inciting injurious stimuli involves predominantly bronchiolar epithelial cells, then phase II is associated with the concentric infiltration of lymphocytes and collagen deposition in the peribronchiolar areas, resulting in the development of chronic bronchiolitis. If, in contrast, the principal target of early damage is the alveolar epithelium, then leukocyte recruitment and matrix deposition during phase II are confined primarily to the interstitial space. Activated lymphocytes then migrate into the airway mucosa and contribute to epithelial injury. As chronic inflammation proceeds to phase III, lung fibroblasts increase in number and contribute to the enhanced deposition of collagen and granulation tissue in and around bronchial structures, ultimately resulting in complete obliteration of small airways and fixed obstructive defects. Similarly, fibroblast proliferation and intraseptal collagen deposition during phase III ultimately results in interstitial thickening, septal fibrosis, significant volume loss, and severe restrictive lung disease.

Clinical and experimental data suggest that the progression to a chronic, profibrotic form of pulmonary toxicity involves the secretion of immunomodulatory proteins, and in this context, tumor necrosis factor (TNF)-α may be a central factor in the triphasic model outlined earlier. Strong evidence for a role of TNF-α in the transition from acute to chronic lung injury comes from a study using transgenic mice with targeted overexpression of TNF-α in the lungs. Early lung histopathology includes a robust leukocytic infiltrate, whereas prolonged exposure to TNF-α results in chronic inflammation and fibrosis [121].

Patients with more severe disease at the time of diagnosis tend to have a poor prognosis; early recognition and treatment may be important to successful outcomes. Thus, increased surveillance for lung dysfunction by serial pulmonary function testing (including an assessment of lung volume, spirometry, and diffusion capacity) for the first 2 years after HCT should be considered whenever feasible. Given the significant morbidity and mortality associated with advanced OLD and RLD, a careful, comprehensive evaluation is recommended once persistent signs or symptoms of pulmonary dysfunction are detected [114,116]. Testing should include a high-resolution computed tomography scan of the chest and bronchoalveolar lavage to exclude opportunistic infections. Lung biopsy also can be quite helpful in making a definitive diagnosis.

Standard therapy for OLD combines enhanced immunosuppression with supportive care, including antimicrobial prophylaxis, bronchodilator therapy, and supplemental oxygen when indicated. Although the treatment for RLD is less well defined, increasing evidence suggests that this form of pulmonary dysfunction also may be immunologically mediated [118]. Unfortunately, the response to multiple agents, including corticosteroids, cyclosporine, tacrolimus, and azathioprine, is limited and tends to occur only early in the course of treatment [108]. The potential role for TNF-α in the pathogenesis of both OLD and RLD suggests that neutralizing agents such as etanercept (Enbrel; Amgen,) may have promise [122]. The

combination of azithromycin, montelukast, and inhaled fluticasone (FAM) in preventing progression of newly diagnosed BOS is currently under investigation [123].

Noninfectious lung injury after allogeneic HCT remains a significant problem. Determining whether the lung is a target of GVHD is crucial. Similarities between the histopathologic features of BO seen in association with OLD after allogeneic HCT and during lung allograft rejection, together with reports of improved lung function with immunosuppression, strongly suggest operative pathways of alloimmune activation. Further research on mechanisms of chronic lung injury after HCT is needed to improve our understanding of this debilitating spectrum of late effects and guide the development of novel therapeutic strategies for treatment and prevention. Studying a triphasic model of chronic, noninfectious lung injury after HCT that involves T cell activation, leukocyte recruitment, and collagen deposition and fibrosis may lead to improvements in therapy. Finally, gaining insight into the factors affecting the anatomic specificity (peribronchiolar versus interstitial) of chronic lung injury and the role of acute inflammation in the initial damage to the alveolar or bronchiolar epithelium will enhance our understanding of posttransplantation pulmonary dysfunction.

CONCLUSIONS

Current data suggest that post-HCT organ complications occur as a result of cellular damage that leads to a cascade of complex events. The degree of cellular damage that results is related to the overall health status, other comorbidities, and baseline organ function of the pre-HCT recipient, with additional impacts related to the intensity of the conditioning regimen, infections, drug exposures, and delayed immune tolerance. The interplay of inflammatory processes and dysregulated cellular repair likely contributes to end-organ fibrosis and dysfunction (Figure 4).

HCT survivors have a high burden of morbidity, especially related to the development of organ-specific late effects after HCT. However, there remain significant gaps in our knowledge of the pathophysiology of therapy-related organ toxicities after HCT. These gaps can be addressed by closely examining disease biology and identifying the patients at greatest risk for these adverse outcomes. In addition, strategies are needed for targeted disease prevention and health promotion efforts for individuals at high risk because of their genetic makeup or specific exposure profile.

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