Published in final edited form as:
Biol Blood Marrow Transplant. 2012 January ; 18(1 Suppl): S184–S188. doi:10.1016/j.bbmt.2011.10.025.

Understanding Chronic GVHD from Different Angles

Bruce Blazar[1], **Eric S. White**[2], and **Daniel Couriel**[3]

[1]Pediatric Blood and Marrow Transplantation Program, University of Minnesota

[2]Division of Pulmonary and Critical Care Medicine, University of Michigan Medical School

[3]Blood and Marrow Transplantation Program, Department of Internal Medicine, University of Michigan Medical School

T CELL:B CELL COOPERATIVITY IN MURINE CHRONIC GVHD

Introduction

Whereas acute graft-versus-host disease (aGVHD) rates have decreased with more intensive GVHD preventive agents and use of single and double umbilical cord blood units as a source of donor cells in adult recipients, significant chronic GVHD (cGVHD) rates unexpectedly have remained high. Moreover, granulocyte colony stimulating factor mobilized peripheral blood stem cell grafts have been associated with an increased overall risk of cGVHD. As such, cGVHD has emerged as 1 of the primary causes of morbidity and mortality following allogeneic hematopoietic stem cell transplantation. Progress in developing cGVHD interventional strategies has been hampered by variable onset and clinical and pathological manifestations of cGVHD, now better defined by the National Institutes of Health (NIH) consensus conference [1], and a dearth of preclinical models that closely mimic the conditions in which cGVHD is generated and manifested.

Although the exact causes of cGVHD remain unknown, higher antibody levels have been associated with autoimmunity and implicated in cGVHD [2,3]. Newly diagnosed patients with extensive cGVHD had elevated soluble B cell activating factor levels and anti-double-strand DNA antibodies were found [4,5], which was associated with higher circulating levels of pregerminal center (GC) B cells and post-GC plasmablasts [6]. B cells from cGVHD patients were hyperresponsive to Toll-like receptor-9 signaling and have up-regulated CD86 levels [7], suggesting an important participatory role for B cells in establishing cGVHD.

Existing cGVHD models simulate pathological manifestations such as increased serum antibodies (typically anti-DNA antibodies), scleroderma, and fibrosis of skin and liver, and the less common immune complex deposition in kidneys and glomerulonephritis [8,9]. Previously, our laboratory has studied the pulmonary dysfunction and aGVHD organ pathology in mice conditioned with high-dose cyclophosphamide (Cy) and lethal total body irradiation and rescued with allogeneic bone marrow and splenocytes [10]. The functional, physiologic, and pathologic assays demonstrated that Cy and total body irradiation conditioned recipients with low numbers of allogeneic T cells developed bronchiolitis obliterans (BO), characterized by airway blockade, peribronchiolar fibroproliferation, and obliteration of bronchioles [11,12]. BO is prevalent in 2% to 3% of hematopoietic stem cell transplanation patients and up to 6% of patients who develop GVHD [13], and has a 5-year

Correspondence and reprint requests: Daniel Couriel, MD. Blood and Marrow Transplantation Program, University of Michigan, Ann Arbor, MI 48109 (deconfer@umdp.org).

survival rate of only 10% [11]. According to the NIH consensus criteria [1], BO is the only pathognomonic manifestation of pulmonary cGVHD.

By using a Cy and low doses of donor T cells, aGVHD was avoided and cGVHD with BO favored. Histologic changes were similar to the findings in human cGVHD [2] with peribronchiolar and perivascular cuffing and infiltration of the airway epithelium. The liver had inflammation and lymphocytic infiltration, along with collagen deposition. The parotid and submandibular salivary glands displayed lymphocytic infiltrates in both the bone marrow and cGVHD groups, likely because of transplantation conditioning. In the tongue, there was a quantifiable difference in the histology and similar profiles of fibrosis seen in the tongue and salivary glands for both groups. The absence of any inflammatory or fibrotic changes in the skin differs from some other models, reinforcing the observation that in mice as in humans, the pathologic manifestations of cGVHD are heterogeneous.

Treatment of steroid refractory cGVHD patients with rituximab, a B cell–depleting anti-CD20 monoclonal antibody, has shown a beneficial role in resolution of the autoimmune disorders such as systemic lupus erythmatosus and rheumatoid arthritis [14] and cGVHD [15–18], with overall response rates of 29% to 36% for oral, hepatic, gastrointestinal, and lung cGVHD, and 60% for cutaneous cGVHD [19] in aggregate data from multiple trials. Thus, we recently undertook studies to identify the presence of $CD4^+$ T helper cells and $B220^+$ B cells in the airways of mice that had BO, tissue-specific antibodies from sera, and alloantibody deposition in the lung and liver of cGVHD recipients. cGVHD development was associated with IgG2c deposition in the lung and liver, abrogated if the donor bone marrow was deficient in mature B cells or incapable of producing antihost reactive IgG. Robust GC formation was seen in mice with cGVHD. Alleviation of symptoms in mice that received B cell–deficient bone marrow confirms the requirement of B cells for lung dysfunction and inflammation and fibrosis in the lung and liver.

Given a role for IgG antibodies, allo- or auto-Ab binding to the cGVHD organs could enable tissue destruction or the pathology could be defined by the specific function of these secreted antibodies. Pathogenic antibody production therefore is likely to be an important inducer of cGVHD, and targeting this specific function of the B cells is an attractive strategy for cGVHD. Because GC B cells display lower susceptibility to rituximab-mediated clearance, probably because they reside in a nonoptimal environment for antibody-based depletion [14], our observation that GC B cells are critical to the development of cGVHD suggests that agents that are more effective at disrupting the GC might be more clinically useful. Treatment with LTβR-Ig, a fusion protein that blocks interactions between LTβR and its ligands, had a direct effect on the symptoms of cGVHD, at least in part by blocking GC formation and suggest that LTβR-Ig could be a potential clinical interventional strategy for prevention and therapy of cGVHD.

TISSUE FIBROSIS: TOO MUCH OF A GOOD THING?

Fibrosis is the end result of a number of inflammatory and other injurious events, resulting in replacement of normal tissue with a dense extracellular matrix (ECM) scar composed primarily of collagens. While some degree of tissue fibrosis is considered protective (e.g. in the setting of cutaneous wound healing), exaggerated or unrelenting ECM deposition with replacement of the normal tissue architecture is considered pathologic. Fibroproliferative disorders as a class involving multiple organs (e.g. cGVHD following hematopoietic stem cell transplant [affecting up to 30% of recipients surviving more than 100 days [20]], scleroderma [estimated to affect 70,000 in the US], idiopathic pulmonary fibrosis [estimated to affect 200,000 in the US], hepatic cirrhosis [estimated to affect up to 400,000 in the US], and renal fibrosis due to diabetic nephropathy and other causes [estimated to affect over

400,000 in the US]) are a major cause of morbidity and mortality. Combined, these disorders alone are conservatively estimated to affect approximately 1 in 300 persons in the United States. When coupled with a host of other disorders in which tissue fibrosis contributes to morbidity (e.g. fibroproliferative acute respiratory distress syndrome, hypersensitivity pneumonitis, solid organ transplant rejection), that estimate is likely to be much greater. Extrapolated globally (especially in developing countries where infectious causes of fibrosis are quite prevalent), fibroproliferative disorders affect a large percentage of the world population. Fibroproliferative diseases are often difficult to treat, primarily because no therapeutic regimens have been identified that will halt the relentless tissue fibrosis. Thus, developing a better understanding of tissue fibrogenesis is likely to make a tremendous impact in global health.

Wound healing occurs by a highly orchestrated, complex process that has been well defined [21]. In general, wound repair occurs in 4 stages which overlap considerably: clotting/coagulation, inflammation, fibroproliferation, and tissue remodeling. The initial injury leads to a local disruption of epithelial and endothelial barriers resulting in the elaboration of inflammatory mediators and extravasation of cells and plasma proteins that serve to achieve hemostasis and provide a provisional fibrin-rich matrix for the influx of inflammatory and other reparative cells [22]. Simultaneously, platelet degranulation provides a local “boost” of vasodilators, growth factors, and ECM proteins that aid in the wound healing response. Inflammatory cell influx occurs next, with polymorphonuclear leukocytes (PMNs) arriving first. Following PMN degranulation, mononuclear cells (macrophages and lymphocytes) arrive next and, along with PMN-derived products, sterilize and remove foreign materials from the wound. This process also results in the elaboration of cytokines and chemokines designed to augment the inflammatory response, to promote angiogenesis (allowing for enhanced nutrient and oxygen delivery to the wound bed), and to recruit fibroblasts to the wound bed [22]. Fibroblast recruitment and transdifferentiation to myofibroblasts (or recruitment of already-differentiated myofibroblasts or fibroblast precursors; this point is still controversial) marks the fibroproliferative stage, with the result being the elaboration of ECM proteins (collagens, fibronectins) to repair the tissue defect. As the fibroproliferative stage matures, myofibroblasts contract the wound edges to allow for efficient re-epithelialization. During the tissue remodeling phase, myofibroblasts are induced to undergo apoptosis, the neo-vessels regress, and the relatively acellular scar tissue remains, ensuring tissue integrity. Following this overly simplified paradigm, tissue fibrosis thus reflects a dysregulated wound healing response which may occur at multiple steps along the way. Moreover, although tissue fibrosis reflects a ‘final common pathway’ after injury, significant variations in tissue mechanics and ECM and cellular specificity of tissues, it is highly likely that the pathogenesis of fibrosis differs widely on an organ-specific basis. Therefore, it is incumbent upon researchers to investigate mechanisms of pathogenic fibrosis in relevant organ systems and models.

Our lab has been interested in the role of the ECM in initiating and propagating a fibrotic response. Historically, ECM deposition and subsequent remodeling have been considered pathologic endpoints in tissue fibrosis. However, ECM remodeling is likely an iterative process in which tissue responses to local injury result in a cyclical process of ECM deposition, altered ECM composition and mechanotransductive properties, release of locally-sequestered and newly-generated growth factors, cellular responses to ECM and growth factors, and further ECM deposition and remodeling [23,24]. Cell behavior, largely influenced by the ECM, dictates whether injury resolves normally or results in progressive fibrosis. In the lung, for example, the ECM strongly influences alveolar re-epithelialization [25], epithelial-mesenchymal transition (EMT) [26], fibroblast migration and proliferation [27,28], fibroblast apoptosis [29], angiogenesis [30] and ECM remodeling [31]. Thus, the ECM is a significant contributor to tissue fibrosis.

With this background in mind, we sought to evaluate whether individual components of the ECM might dictate fibrotic responses to injury. One such ECM component, fibronectin, is a particularly attractive target based on data showing an absolute necessity for fibronectin in development and wound repair [32]. Fibronectins are ubiquitous glycoproteins found in plasma and in the ECM. The proteins consist of two similar non-identical monomers, each roughly 250 kDa, which are joined by disulfide bonds at their C-termini. Each monomer is composed of a series of tightly folded homologous amino acid repeats or domains, termed Type I, II, and III. Although arising from a single gene, several variants of fibronectin are formed by alternative splicing of the pre-mRNA at three separate positions: the Extra Type III Domain A (EDA) and Extra Type III Domain B (EDB), which are each independently included or excluded [33], and a V (for variable) region that undergoes more complex splicing to produce 5 separate variants, resulting in up to 20 potentially different fibronectin forms in humans [34]. On the basis of solubility, however, fibronectin can be divided into 2 forms - soluble plasma fibronectin (pFn) and less-soluble or insoluble cellular fibronectin (cFn) [35]. pFn is primarily synthesized by hepatocytes and excludes the EDA and EDB domains but retains variable V region splicing [34]. Conversely, cFn is produced by epithelial and mesenchymal cells and is characterized by the inclusion of EDA or EDB (or both) in addition to the variable V region splicing [32]. cFn is also stored in platelet -granules and is released following wounding by platelet degranulation [36]. The EDA and EDB domains are typically incorporated into cFn in large quantities during embryonic development and in malignancies, but at very low levels or not at all in uninjured adult tissues [33].

Prior data suggested that EDA cFN is elaborated in the lung of patients with idiopathic pulmonary fibrosis, a relentless fibrosing disorder of the lung that has no known effective therapies [37]. Moreover, the spatial location of EDA cFN, nestled between fibroblasts and collagen fibers within the lung [38], suggested that EDA cFN may be present prior to collagen deposition. Taking advantage of transgenic animals lacking the EDA exon [39], our group sought to evaluate the role of EDA cFN in lung fibrosis using a standard bleomycin-induced lung fibrosis model. We found that EDA-null mice failed to develop significant fibrosis following bleomycin challenge as compared to wild-type littermates, and that this, in part, may have been due to impaired activation of the pro-fibrotic cytokine TGF-b [31]. Similar results have been found in EDA-deficient mice following myocardial infarction [40], in an asthma model [41], and in the fibrosis of chronic cardiac allograft rejection [42]. These data suggest an active role of EDA cFN in tissue fibrosis.

Intriguingly, EDA cFN may also act as a plasma biomarker of fibrotic diseases. Since EDA cFN is not secreted into the circulation by hepatocytes [43], circulating EDA cFN may reflect ongoing tissue remodeling in fibrosing diseases. Supporting this hypothesis, studies from several groups have documented an elevation of plasma EDA cFN in patients with cGVHD [44], rheumatoid arthritis [45], and diabetes [46], as well as in the plasma of mice with chronic rejection following cardiac transplantation [42]. Collectively, these data suggest that ECM is an active contributor to tissue fibrosis and may be a viable biomarker for fibrotic diseases. Of course, further study is necessary to determine whether EDA cFN is a sensitive biomarker of disease severity or progression, but these data suggest that investigating the ECM in fibrotic diseases may provide new insight into disease pathogenesis.

CHRONIC GVHD: THE CLINICAL PERSPECTIVE

Introduction

Chronic GVHD is a highly complex and polymorphic disease, with a largely unknown pathophysiology. In the last decade, transplant clinicians became increasingly aware that the

traditional chronologic diagnostic criteria failed to address this complexity, and that a substantial number of patients diagnosed with cGVHD had manifestations of aGVHD after day 100. Most of these patients would transition, usually at some point during the first year posttransplantation into what we now consider cGVHD according to NIH criteria. About a one-third of the cases of cGVHD will occur without a prior history of aGVHD. Others will develop overlapping features of both aGVHD and cGVHD for months or years. The variability of clinical presentations, from the patient with a lichenoid form to the 1 that is immobile because of advanced sclerosis, demonstrates that cGVHD encompasses more than just 1 clinical syndrome. Furthermore, the number of organs affected is different and so far unpredictable for different patients. Finally, depending on the manifestation of the disease, what we see as clinicians may not be as clinically meaningful as the patient-reported outcomes. Thus, depending on our expectations, 1 perfect scoring system may not be realistic.

A Scoring System for cGVHD

The NIH Consensus was the first attempt to resolve the diagnostic complexity of cGVHD, providing a clinical rather than chronologic framework, and discriminating acute versus chronic manifestations [1]. The NIH Consensus also produced a scoring and assessment of response systems, mostly based on expert opinion [1,20]. Both systems are based on a combination of extensive description, as well as objective and subjective measures. The relative weight of each of these types of measures varies in each organ, although this variation is still not based on data correlating clinical descriptions with more objective measures or outcomes. The objective is that both the scoring and assessment of response systems would provide more comprehensive prognostic and evaluative measures. Different groups have focused on prognosis, correlating the NIH Consensus scoring system with different outcomes. Severe cGVHD may impact survival, particularly when compared with mild or no cGVHD [21–26]. Additionally, the existence of an aGVHD component as late aGVHD in the form of “overlap syndrome” may also confer a poorer prognosis [21,23,26,27]. Severity of cGVHD can also influence duration of immunosuppression and recurrence of cGVHD. All of these findings need to be confirmed prospectively, ideally with the inclusion of patient-reported outcomes, which may help to better characterize prognostic subsets [28,29].

Common Problems in Diagnosis, Scoring, and Follow-up

This section includes case presentations of challenging and not uncommon situations encountered in clinical practice.

Acute or chronic?—One of the major achievements of the NIH Consensus has been the distinction between acute and chronic clinical manifestations of cGVHD, independent of chronology. This validated and formalized the category of patents with “late” aGVHD, or aGVHD beyond day 100. Thus, a patient with diarrhea secondary to aGVHD on day 99 posttransplantation, is not reclassified as having cGVHD after day 100. The question that remains is for how long a period of time an aGVHD manifestation should be considered acute. In the absence of diagnostic manifestations of cGVHD, should diarrhea secondary to GVHD, which presents years after transplantation, still be considered aGVHD? Where would such patient fit in our current scoring system?

Scoring GVHD of the lung—Chronic GVHD of the lung or BO is 1 of the most difficult situations to diagnose and to score. Open lung biopsies in transplant patients where the diagnosis is suspected can be risky and difficult to justify outside a clinical trial setting. Therefore, we generally rely on a combination of clinical, spirometric, and radio-logic findings with at least an additional distinctive manifestation of cGVHD in another organ.

Patients with preexisting lung disease, infections, or those without additional manifestations of cGVHD present diagnostic and treatment challenges.

When severe becomes not so severe—The criteria for severity of cGVHD may not always reflect our clinical impression. This is particularly clear in certain organs and situations. A relatively frequent and striking example is isolated severe ocular cGVHD, where dryness can be almost completely alleviated by special eyewear. In this case, cGVHD is overall severe based on NIH Consensus criteria, independent of the positive effects of intervention. Limited sclerotic cGVHD of the skin without any functional impact presents a similar challenge.

Disease activity and scoring system—How does our scoring system account for long-term survivors with permanent sequelae of cGVHD, without any major functional impact and off all immunosuppression? In other words, at what point do we stop scoring our patients for cGVHD?

Conclusions

The last decade has seen an explosion of interest in the problems associated with survival after hematopoietic stem cell transplantation, particularly cGVHD. The NIH Consensus has provided for the first time a systematic approach to a problem that we had recognized as complex for years. This was also the starting point of national and international collaborations, interest groups, and other efforts directed to the common goal of improving the lives of our survivors. The next step is to validate our starting point, assessing the validity and reliability of our measurements, their ability to prognosticate, and to provide useful day-to-day information on clinical changes. Because of the clinical complexity of the disease, accurate assessment and scoring will require the contribution of biomarker and translational research.

Acknowledgments

Financial disclosure: Dr. Couriel is a speaker for Therakos, Inc and Merck, Inc, and is on the advisory board for Merck and Therakos.

REFERENCES

1. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant. 2005; 11:945–956. [PubMed: 16338616]
2. Baird K, Cooke K, Schultz KR. Chronic graft-versus-host disease (GVHD) in children. Pediatr Clin North Am. 2010; 57:297–322. [PubMed: 20307722]
3. Kapur R, Ebeling S, Hagenbeek A. B-cell involvement in chronic graft-versus-host disease. Haematologica. 2008; 93:1702–1711. [PubMed: 18728020]
4. Fujii H, Cuvelier G, She K, et al. Biomarkers in newly diagnosed pediatric-extensive chronic graft-versus-host disease: a report from the Children's Oncology Group. Blood. 2008; 111:3276–3285. [PubMed: 17925486]
5. Sarantopoulos S, Stevenson KE, Kim HT, et al. High levels of B-cell activating factor in patients with active chronic graft-versus-host disease. Clin Cancer Res. 2007; 13:6107–6114. [PubMed: 17947475]
6. Sarantopoulos S, Stevenson KE, Kim HT, et al. Altered B-cell homeostasis and excess BAFF in human chronic graft-versus-host disease. Blood. 2009; 113:3865–3874. [PubMed: 19168788]
7. She K, Gilman AL, Aslanian S, et al. Altered Toll-like receptor 9 responses in circulating B cells at the onset of extensive chronic graft-versus-host disease. Biol Blood Marrow Transplant. 2007; 13:386–397. [PubMed: 17382246]

8. Zhang C, Todorov I, Zhang Z, et al. Donor CD4+ T and B cells in transplants induce chronic graft-versus-host disease with autoimmune manifestations. Blood. 2006; 107:2993–3001. [PubMed: 16352808]
9. Chu YW, Gress RE. Murine models of chronic graft-versus-host disease: insights and unresolved issues. Biol Blood Marrow Transplant. 2008; 14:365–378. [PubMed: 18342778]
10. Panoskaltsis-Mortari A, Tram KV, Price AP, Wendt CH, Blazar BR. A new murine model for bronchiolitis obliterans post-bone marrow transplant. Am J Respir Crit Care Med. 2007; 176:713–723. [PubMed: 17575098]
11. Dudek AZ, Mahaseth H, DeFor TE, Weisdorf DJ. Bronchiolitis obliterans in chronic graft-versus-host disease: analysis of risk factors and treatment outcomes. Biol Blood Marrow Transplant. 2003; 9:657–666. [PubMed: 14569562]
12. Al-Githmi I, Batawil N, Shigemura N, et al. Bronchiolitis obliterans following lung transplantation. Eur J Cardiothorac Surg. 2006; 30:846–851. [PubMed: 17055283]
13. Chien JW, Duncan S, Williams KM, Pavletic SZ. Bronchiolitis obliterans syndrome after allogeneic hematopoietic stem cell transplantation-an increasingly recognized manifestation of chronic graft-versus-host disease. Biol Blood Marrow Transplant. 2010; 16(Suppl):S106–S114. [PubMed: 19896545]
14. Browning JL. B cells move to centre stage: novel opportunities for autoimmune disease treatment. Nat Rev Drug Discov. 2006; 5:564–576. [PubMed: 16816838]
15. Ratanatharathorn V, Ayash L, Reynolds C, et al. Treatment of chronic graft-versus-host disease with anti-CD20 chimericmonoclonal antibody. Biol Blood Marrow Transplant. 2003; 9:505–511. [PubMed: 12931119]
16. Cutler C, Miklos D, Kim HT, et al. Rituximab for steroid-refractory chronic graft-versus-host disease. Blood. 2006; 108:756–762. [PubMed: 16551963]
17. Canninga-van Dijk MR, van der Straaten HM, Fijnheer R, et al. Anti-CD20 monoclonal antibody treatment in 6 patients with therapy-refractory chronic graft-versus-host disease. Blood. 2004; 104:2603–2606. [PubMed: 15251978]
18. Miklos DB, Kim HT, Miller KH, et al. Antibody responses to H-Y minor histocompatibility antigens correlate with chronic graft-versus-host disease and disease remission. Blood. 2005; 105:2973–2978. [PubMed: 15613541]
19. Kharfan-Dabaja MA, Mhaskar AR, Djulbegovic B, Cutler C, Mohty M, Kumar A. Efficacy of rituximab in the setting of steroid-refractory chronic graft-versus-host disease: a systematic review and meta-analysis. Biol Blood Marrow Transplant. 2009; 15:1005–1013. [PubMed: 19660713]
20. Pavletic SZ, Martin P, Lee SJ, et al. Measuring therapeutic response in chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: IV. Response Criteria Working Group report. Biol Blood Marrow Transplant. 2006; 12:252–266. [PubMed: 16503494]
21. Arora M, Nagaraj S, Witte J, et al. New classification of chronic GVHD: added clarity from the consensus diagnoses. Bone Marrow Transplant. 2009; 43:149–153. [PubMed: 18794869]
22. Cho BS, Min CK, Eom KS, et al. Feasibility of NIH consensus criteria for chronic graft-versus-host disease. Leukemia. 2009; 23:78–84. [PubMed: 18830253]
23. Kim DY, Lee JH, Lee JH, et al. Reevaluation of the National Institutes of Health criteria for classification and scoring of chronic GVHD. Bone Marrow Transplant. 2010; 45:1174–1180. [PubMed: 19915630]
24. Perez-Simon JA, Encinas C, Silva F, et al. Prognostic factors of chronic graft-versus-host disease following allogeneic peripheral blood stem cell transplantation: the national institutes health scale plus the type of onset can predict survival rates and the duration of immunosuppressive therapy. Biol Blood Marrow Transplant. 2008; 14:1163–1171. [PubMed: 18804047]
25. Pidala J, Kim J, Anasetti C, et al. NIH Consensus chronic graft vs. host disease global severity is associated with overall survival and non-relapse mortality. Haematol. 2011; 96:1678–1684.
26. Sato T, Ichinohe T, Kanda J, et al. Clinical significance of subcategory and severity of chronic graft-versus-host disease evaluated by National Institutes of Health consensus criteria. Int J Hematol. 2011; 93:532–541. [PubMed: 21465116]

27. Jagasia M, Giglia J, Chinratanalab W, et al. Incidence and outcome of chronic graft-versus-host disease using National Institutes of Health consensus criteria. Biol Blood Marrow Transplant. 2007; 13:1207–1215. [PubMed: 17889358]

28. Lee S, Cook EF, Soiffer R, Antin JH. Development and validation of a scale to measure symptoms of chronic graft-versus-host disease. Biol Blood Marrow Transplant. 2002; 8:444–452. [PubMed: 12234170]

29. Pidala J, Kurland B, Chai X, et al. Patient-reported quality of life is associated with severity of chronic graft-versus-host disease as measured by NIH criteria: report on baseline data from the Chronic GVHD Consortium. Blood. 2011; 117:4651–4657. [PubMed: 21355084]