

Clinical characterization and outcomes in chronic graft-versus-host disease

Pavlečić, Steven Živko

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**UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE**

STEVEN ŽIVKO PAVLETIĆ

**CLINICAL CHARACTERIZATION AND OUTCOMES IN
CHRONIC GRAFT-VERSUS-HOST DISEASE**

DOCTORAL DISSERTATION

SPLIT, JUNE 2023

**UNIVERSITY OF SPLIT
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DOCTORAL DISSERTATION

MENTOR:

PROFESSOR OZREN POLAŠEK

SPLIT, JUNE 2023

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Thesis supervisor: Professor Ozren Polašek, MD, MPH, PhD

Table of Contents

1. LIST OF ABBREVIATIONS	d
2. INTRODUCTION	1
3. RESEARCH AIMS	8
4. SCIENTIFIC CONTRIBUTION OF THE POOLED RESULTS	14
4.1. Paper 1	14
4.2. Paper 2	19
4.3. Paper 3	22
4.4. Paper 4	27
5. COPIES OF THE POOLED PAPERS	31
6. REFERENCES	32
7.ABSTRACT	35
8.CURRICULUM VITAE	38

1. LIST OF ABBREVIATIONS

aGVHD	acute graft-versus-host disease
ALL	acute lymphocytic leukemia
alloHSCT	allogeneic hematopoietic stem cell transplantation
alloPBSCT	allogeneic peripheral blood cell transplantation
alloBMT	allogeneic bone marrow transplantation
AML	acute myelocytic leukemia
cGVHD	chronic graft-versus-host disease
CML	chronic myelogenous leukemia
CMV	cytomegalovirus
GM-CSF	granulocyte-macrophage colony-stimulating factor
GVT	graft-versus-tumour effect
HLA	human leukocyte antigen
IRB	institutional review boards
MDS	myelodysplastic syndromes
NHL	non-Hodgkin lymphoma
NIH	National Institutes of Health
SD	standard deviation
TCD	T cells from the marrow graft

2. INTRODUCTION

This research focuses on Chronic Graft-versus-Host disease (cGVHD), a new disease in medicine caused by complications of allogeneic hematopoietic stem cell transplantation (alloHSCT) in patients with hematologic malignancy or another life-threatening disease of the bone marrow. About 10 thousand patients receive alloHSCT annually in the United States (about 30,000 worldwide), and about half develop cGVHD [1]. The first modern alloHSCTs were performed in 1968 and 1969 in the USA from HLA-matched siblings [2]. First HLA-matched alloHSCT was performed in Croatia in 1983 [3]. E.D. Thomas of Seattle received Nobel Prize for medicine in 1990 for developing alloHSCT to cure leukemia and aplastic anemia [2]. Many allotransplants have steadily grown worldwide since the 1980s due to expanding donor sources (unrelated donors, umbilical cords, haploidentical related donors), increasing safety, efficacy, and practicality [4].

Therapeutic effects of alloHSCT are mediated by donor T cells which target histocompatibility antigens on recipient malignant and non-malignant cells and tissues. The clinical manifestation of these recipient-directed immunological reactions is acute and chronic GVHD. While acute GVHD occurs typically within the first 1-2 months after alloHSCT and is mediated by the infused alloreactive T-cells affecting three key targets organs (skin, gastrointestinal tract, and liver), cGVHD occurs later, typically 6-12 months after transplant and is mediated by a complex still poorly understood processes of disordered immune system regulation and maturation (**Figure 1**)[1, 5].

Chronic GVHD Syndrome per NIH Criteria

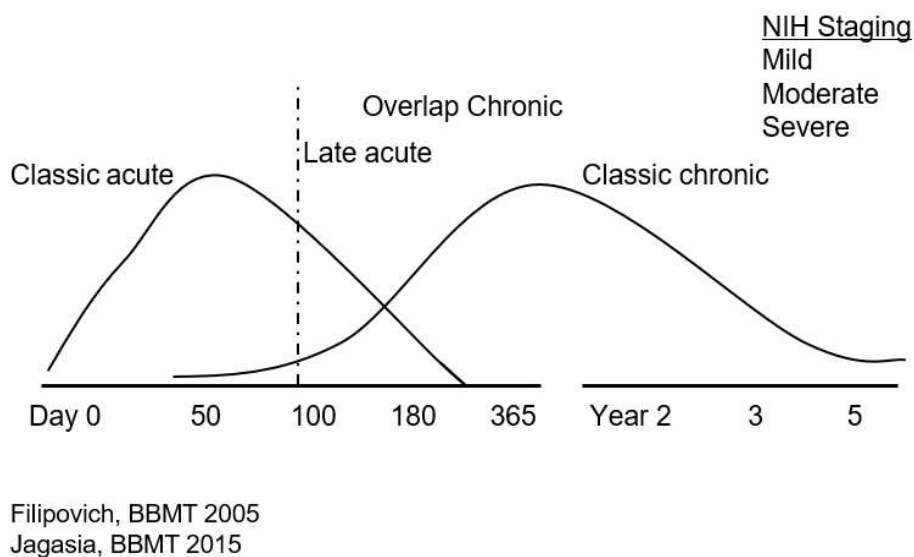


Figure 1. Chronic graft-versus-host disease timeline after infusion of allogeneic HSCT (NCI)

Chronic Graft-versus-host disease (cGVHD) is a systemic, multi-organ disease and can involve the skin, eyes, mouth, GI tract, lungs, liver, genitals, and joints/fascia. Severe cGVHD is debilitating for patients, with a significant influence on patient quality of life (QoL), and with high rates of associated morbidity and mortality (**Figure 2, Figure 3**) [6, 7]. The first clinical descriptions of cGVHD in humans were reported in the late 1970s, resembling various autoimmune diseases such as systemic sclerosis, lupus or Sjogren Syndrome [8, 9]. Later it was observed that such patients had fewer leukemia relapses after alloHSCT (e.g. “graft-versus-leukaemia/tumor effect”) [10-12]. The steadily growing number of allogeneic transplants and changes in transplant practices (more unrelated and mismatched donors, older patients, increased use of peripheral blood instead of bone marrow, use of donor leukocyte infusions) have resulted in more transplant survivors with cGVHD [13].

Chronic Graft-versus-Host disease – main complication after allogeneic hematopoietic cell transplantation

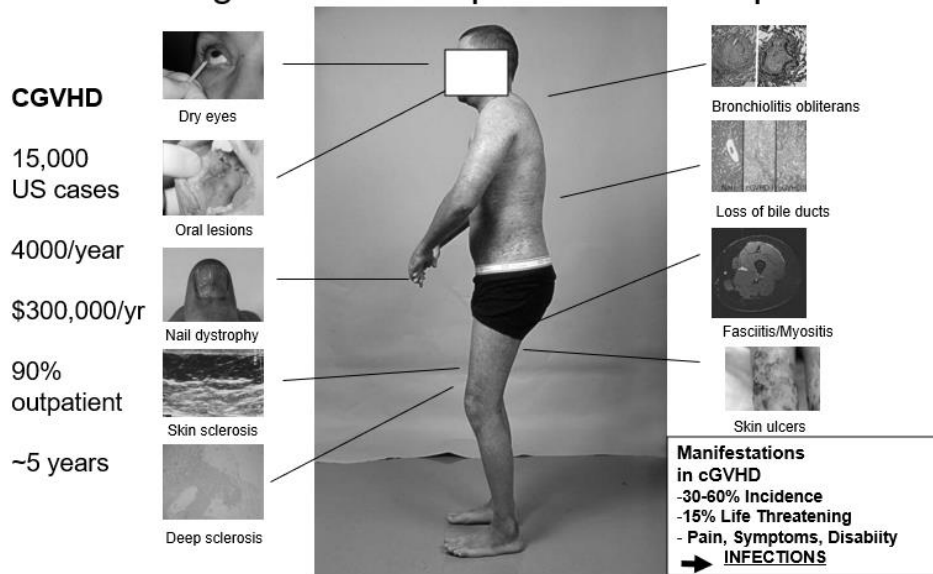


Figure 2. Manifestations of chronic graft-versus-host disease (NCI)

Validation of NIH cGVHD staging criteria: Severe NIH Global stage defines significantly worse survival and higher NRM cGVHD Consortium, N=298

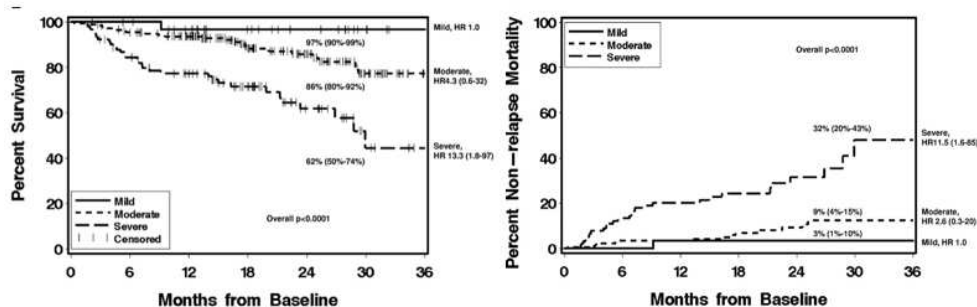


Figure 3. NIH severity scoring defines chronic GVHD severity predicts survival and transplant related mortality after allogeneic HSCT [7]

Chronic GVHD pathophysiology is characterized by immune dysregulation, chronic inflammation, loss of immune tolerance, and fibrosis resulting from impaired tissue repair (**Figure 4**) [1, 14]. Immune cell subsets seen in cGVHD patients favor skewed T-cell subset populations with increased T-helper 1 (Th1), Th17 and follicular Th cells, as well as B-cell dysregulation. Pro-inflammatory cytokines, such as interleukin-17 (IL-17), IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-21, and interferon- γ (IFN γ) also dominate the cytokine milieu and lead to many deleterious downstream effects. Decreased levels of regulatory T-cells (Tregs) contribute to defective immune tolerance. Main players leading to impaired tissue repair and scarring include macrophages and fibroblasts driven by high levels of transforming growth factor β (TGF- β) and tumor necrosis factor α (TNF α).

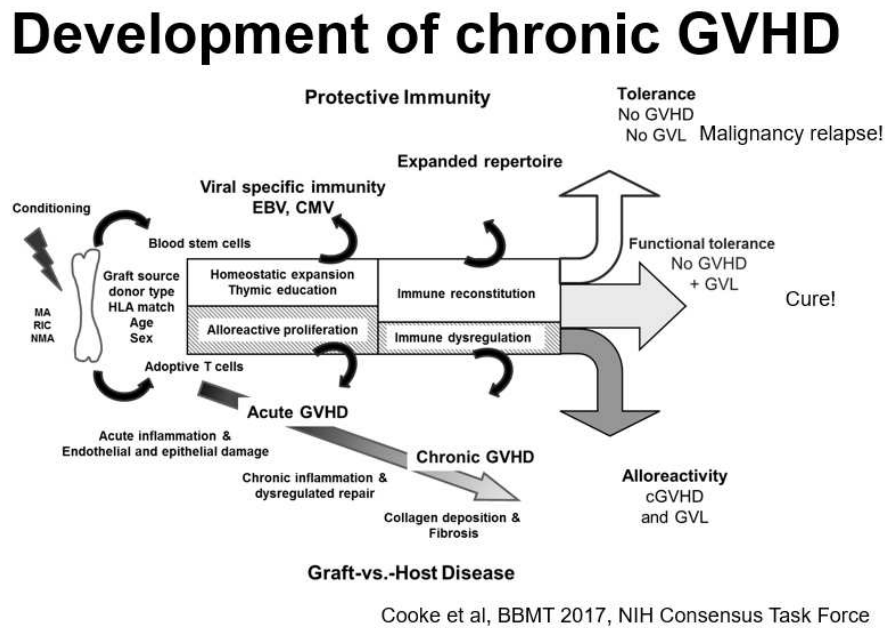


Figure 4. Pathophysiology of chronic graft-versus-host disease [13]

In the early 2000s, it became clear there was no progress in treatment and understanding of the biology of cGVHD. There were no standardized criteria for diagnosis, staging, measurements of clinical response or design of clinical trials. There were no established research networks, no FDA-approved drugs or non-existing clinical drug development pathways. In 2003 the cGVHD study group was established at the National Cancer Institute, National Institutes of Health, in Bethesda, Maryland, under the leadership of Dr Steven Zivko Pavletic, MD, to focus clinical research on cGVHD.

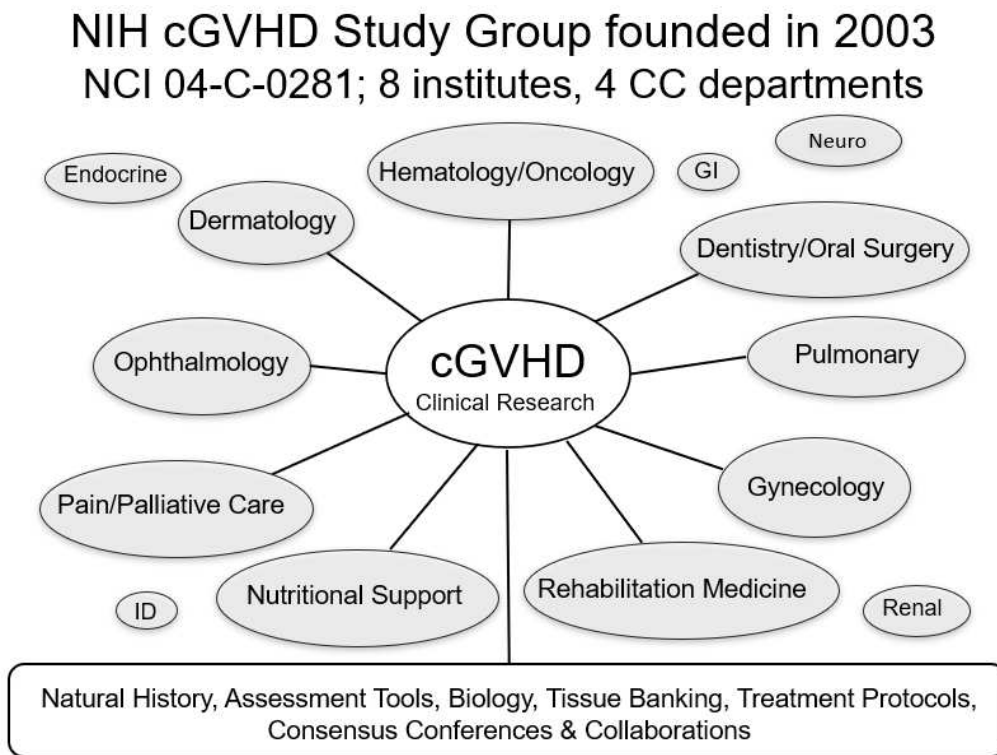


Figure 5. NIH Chronic GVHD Multidisciplinary Study Group Team Approach



Figure 6. The original NIH Chronic GVHD Study Group photo. The team was instrumental in establishing novel and standardized disease evaluation and research approaches.

This project was initiated under the NCI 04-C-0281 cGVHD protocol “Natural history study of clinical and biological factors determining outcomes in cGVHD (NCT00092235), principal investigator Steven Zivko Pavletic. There were four key objectives: 1. Establish a multidisciplinary clinic to develop standardized cGVHD clinical evaluation tools, 2. Obtain peripheral blood and tissue (skin, oral mucosa) samples to study cGVHD biology, 3. Develop new systemic and topical therapies for cGVHD, and 4. Pursue national and international collaboration through a series of cGVHD NIH consensus conferences. This protocol resulted in more than 120 publications in peer-reviewed medical journals since 2004. The NIH consensus conferences in 2005 and 2014 produced 13 key publications; some are among the most referenced articles in the clinical bone marrow transplant literature (12/18/2022 Google scholar citations = 8578) [6, 14-25]. Dr Pavletic was the chair of these consensus projects and authored or coauthored all papers (Dr Pavletic H-index 75, Google Scholar accessed on December 18, 2022). All these illustrate the impact of this work on the field.

This article-based doctoral dissertation focuses on four representative manuscripts published by Dr. Pavletic as the first author between 2005 and 2021 [18, 26-28]. The first two papers describe some key clinical characteristics and prognostic factors for outcomes in patients with cGVHD, one from a single center, the other from a randomized controlled clinical trial. The third paper results from the year-and-a-half-long iterative processes of organ-focused working groups resulting in a pioneering definition of the NIH cGVHD response criteria used as a foundation for the first in history approval of a treatment for cGVHD by the Food and Drug Administration in 2017. The fourth paper overviews the most recent 2020 NIH cGVHD consensus project, which Dr Pavletic chaired.

3. RESEARCH AIMS

The overarching hypothesis is that better characterization of cGVHD and standardization of research tools will lead to better research and ultimately improve clinical outcomes in cGVHD.

Specific Aim 1

To determine the influence of ex vivo T-cell depletion and other factors on the incidence of cGVHD and survival in patients after myeloablative alloHSCT from HLA-matched unrelated donors. The hypothesis is that T-cell depletion of bone marrow grafts would result in a lower incidence of both acute and cGVHD [26].

Specific Aim 2

To determine prognostic factors for cGVHD incidence and survival in patients who received myeloablative alloHSCT from an HLA-matched related donor. The hypothesis is that such prognostic factors may differ between peripheral blood and bone marrow grafts [27].

Specific Aim 3

To determine a set of practical measures through an iterative expert opinion process which could produce standardized criteria for quantitative measurement of therapeutic response in cGVHD. The hypothesis is that such criteria would serve faster development of novel therapeutics [18].

Specific Aim 4

To determine gaps in the current knowledge about cGVHD and define novel strategies for personalized approaches to therapy and prevention. The hypothesis is that such a communal approach will result in radically new strategies to address cGVHD [28].

Specific Aim 1 Methods

This matched unrelated donor marrow transplantation trial included 15 participating transplantation centers across the USA. Between 3/1995 and 10/2000, 410 patients with hematologic malignancies were randomized; 203 received T-cell-depleted marrow and cyclosporine (TCD arm) and 207 received methotrexate and cyclosporine. The institutional review boards (IRBs) approved the study protocol at each transplantation center, and all patients signed IRB-approved consent forms before treatment. Of the 410 patients randomized, 5 died before undergoing transplantation (TCD, n=2; M/C, n=3), and one patient underwent transplantation two years later. The median recipient age was 31.2 years (0.5-55.6 years). Diagnoses included chronic myelogenous leukemia (CML; n=182), acute myelocytic leukemia (AML; n=103), acute lymphocytic leukemia (ALL; n= 88), myelodysplastic syndromes (MDS; n=23), non-Hodgkin lymphoma (NHL; n=3), and other leukemia (n=11). The mean infused CD3+ cell doses were 2.8 +/-12.9 (standard deviation [SD]) x10⁶/kg and 30.1 x 22.0 +/- x10⁶/kg in the TCD and M/C arms, respectively. The mean infused CD34+ cell doses were 2.0 +/- 1.8 x10⁶/kg and 3.8 +/- 3.4 x10⁶/kg in the TCD and M/C arms, respectively. The protocol required donors to be selected based on matching HLA-A and -B determined by serologic level typing and HLA-DRB1 determined by high-resolution molecular typing. Overall, 298 (73%) patients received an HLA 6 of 6 match. In patients with an HLA 5 of 6 match, 10% were mismatched at HLA-A (n =40), 9% at HLA-B (n =36), and 9% at HLA-DRB1 (n =36). The median donor age was 36 years (range 19-59 years); 61% of donors were male.

Two methods of TCD were used, counterflow centrifugal elutriation (Beckman, Palo Alto, CA), a physical method of separating T cells from hematopoietic stem and progenitor cells, and T10B9 (MEDI-500; Medimmune, Gaithersburg, MD), an antibody method of targeting the $\alpha\beta$ subunit of the T-cell receptor, which lyses bound cells in the presence of rabbit complement.[29, 30] Recipients of TCD received additional therapy in order to promote engraftment. Patients who received marrow T-cell depleted by T10B9 plus complement (n =134) received conditioning consisting of 1410 cGy fractionated total body irradiation (TBI) over three days, 9 gm/m² cytarabine over three days, and 100 mg/kg cyclophosphamide over two days.

Patients who received TCD by elutriation (n =67) received a conditioning regimen consisting of 1320 cGy to 1375 cGy TBI over four days, 120 mg/kg cyclophosphamide over 2 days, and 60 mg/kg per day equine antithymocyte globulin over 2 days. Patients randomized to M/C received 1320 cGy to 1375 cGy fractionated TBI and 120 mg/kg cyclophosphamide over 2 days. For GVHD prophylaxis, all patients received cyclosporine after transplantation. Patients on the M/C arm also received intravenous methotrexate: 15 mg/m² on day 1 and 10 mg/m² on days 3, 6, and 11.

The primary endpoint of the analysis was the incidence of any stage (extensive or limited) cGVHD. To describe the actual risk of cGVHD at the time of transplantation, the complement of the Kaplan-Meier (1-KM) and the cumulative incidence estimate (CINC) for cGVHD were determined. Kaplan-Meier estimates were used to estimate survival, and differences between groups were compared using the log-rank statistic. The Cox proportional hazards model with time-dependent covariates was used to create prognostic models considering multiple variables. Variables considered were: treatment arm; TCD method; transplantation center; total CD3+, CD34+, and nucleated cell doses; recipient and donor demographics; primary disease; risk status; degree of HLA match; recipient and donor cytomegalovirus (CMV) serologic status; median days to neutrophil engraftment; previous maximum aGVHD grade; and organs involved. Additional variables for the analyses of patients diagnosed with cGVHD included Karnofsky-Lansky performance score, serum bilirubin level and platelet count, and the organs involved. Incidence of relapse was estimated, with death in remission as a competing risk. The time to terminate all systemic immunosuppression was estimated with death, while receiving immunosuppression was considered a competing risk. The median recipient age was 31.2 years (range, 0.5-55.6 years). The median donor age was 36 years (range, 19-59 years); 61% of donors were male. Data forms were prospectively collected at baseline, 100 days, six months, one year, and annually [26].

Specific Aim 2 Methods

Adult patients with hematologic malignancy consented to participate in the University of Nebraska Medical Center IRB-approved studies of high-dose therapy and alloHSCT from an HLA-matched related donor. Eighty-seven patients received alloPBSCT between 12/1994 and 11/1998 and 75 alloBMT between 1/1990 and 9/1998 and survived at least 100 days post-transplant. Peripheral blood stem cells were mobilized from normal donors with recombinant G-CSF (filgrastim), collected with leukapheresis, and cryopreserved. Bone marrow was harvested using standard methods and immediately infused. Conditioning regimens included cyclophosphamide (120 mg/kg) and total body irradiation (1,200 cGy), with or without etoposide (1,800 mg/m²). GVHD prophylaxis consisted of cyclosporine and methotrexate. The cGVHD information was retrieved from patients' records using pre-designed data forms.

Patients were evaluated for cGVHD every three months until two years post-transplant and then yearly. This study examined prognostic factors for cGVHD onset, survival, and mortality in a group of long-term survivors after alloPBSCT who received HLA-matched related donor grafts. To determine whether prognostic factors identified in alloPBSCT may be applicable after alloBMT, the prognostic factors were tested on an independent sample of alloBMT patients who received identical GVHD prophylaxis regimens.

The primary endpoints of this analysis were (a) incidence of cGVHD, (b) impact of cGVHD on overall survival, (c) overall survival following cGVHD, and (d) incidence of cGVHD-specific mortality (deaths in patients with cGVHD without post-transplant malignancy relapse). Log-rank tests were used to compare the distributions of time to event variables. Univariate Cox regression analysis was used to estimate relative risks and 95% confidence intervals for risk factors of incidence of cGVHD, overall survival, overall survival following cGVHD, and cGVHD-specific mortality for alloPBSCT cases. Overall survival following cGVHD was calculated as the time from the date of diagnosis of cGVHD to death from any cause or date of last contact. Multivariate models were fit with Cox stepwise regression to the alloPBSCT data for all four primary outcomes. The significance level for variables to be entered and removed from the models was 0.05. The set of significant predictors in the alloPBSCT

setting was then fit to Cox models of the alloBMT data. To investigate the impact of cGVHD on overall survival, cGHVD is treated as a time-dependent variable after adjusting for other significant predictors of overall survival. The Kaplan–Meier method was used to estimate overall survival and survival distributions following cGVHD [27].

Specific Aim 3 Methods

This work took place from June 2004 to January 2006 and is based on a series of iterative meetings, a planning conference, and a broad consensus of national and international experts. The Working Group consisted of 38 experts of various specialities (adult and pediatric hematology, histopathology, dermatology, gastroenterology, dentistry, pain and palliative care, pulmonology, ophthalmology, rehabilitation medicine, rheumatology, outcome research, statistics, and regulatory agency) who determined face validity of proposed cGVHD response measures.[18] This Working Group process began by reviewing instruments currently used by hematopoietic stem cell transplantation physicians at Johns Hopkins, Children’s Oncology Group, Fred Hutchinson Cancer Research Center, Harvard University, University of Minnesota, and National Institutes of Health.

This final paper summarizes proposed measures and criteria for assessing outcomes in clinical trials involving patients with chronic GVHD. The measures and criteria do not necessarily reflect practices that might apply to routine patient care or to trials with limited resources. The measures and response criteria were developed to meet certain requirements:

1. The instruments should be easy to use by both transplantation and nontransplantation care providers and should be limited to testing methods that are available in the outpatient setting.
2. The criteria should be adaptable for use in adults and in children.
3. The instrument should focus on the most important and most common manifestations of cGVHD and should not be designed to characterize all possible clinical manifestations.
4. Development should focus on quantitative measures as much as possible.

5. Measurements of symptoms, signs, global ratings, function, quality of life, or performance status should be made separately, and scales with established psychometric characteristics and desirable measurement properties should be used whenever possible.
6. With appropriate refinements and reliability and validation assessments, these tools should be suitable for use in clinical trials where the goals are to improve patient outcomes or to obtain FDA and other regulatory approvals.

The paper had three additional goals: (1) to propose provisional definitions of complete response, partial response, and disease progression for each organ and overall response; (2) to suggest appropriate strategies for using short-term endpoints in therapeutic clinical trials; and (3) to outline future research directions.

Specific Aim 4 Methods

To address challenges in a rapidly changing field of cGVHD, a third NIH Consensus Development Project on Criteria for Clinical Trials was initiated in November 2019 after receiving funding support from the National Cancer Institute. The four working groups were charged to “think outside the box,” reexamine accomplishments to date, identify gaps in the field of chronic GVHD and allogeneic HCT, and define the next steps that should be taken to advance the field in a fundamentally new way. Five preliminary manuscripts were written between November 2019 and November 2020. Due to the COVID-19 pandemic, the third NIH Chronic GVHD Consensus Conference was held as a virtual meeting over three days through six 2-hour sessions from November 18 to 20, 2020, with 850 registered participants. The four working groups were created to encourage global engagement in the cGVHD topic (prevention, early diagnosis/pre-emption, therapy, highly morbid entities). Groups worked individually to review the relevant literature and create the initial draft of the paper. Two iterative rounds of comments from the Steering Committee were collected before the November 2020 Consensus Conference. Based on additional comments from Conference participants and a 30-day public comment period, this paper and five additional reports were further revised for submission monthly staggered schedule from February to June 2021 [28, 31-35].

4. SCIENTIFIC CONTRIBUTION OF THE POOLED RESULTS

4.1. Paper 1

One of the major obstacles to the wider use of alloHSCT has been the limited availability of HLA-matched sibling donors. During the 1990s, unrelated volunteer marrow donors rapidly expanded through the growth of the National Marrow Donor Program registry [4]. This made alloHSCT available to more patients but exposed them to higher acute and chronic GVHD risks. However, greater donor-recipient genetic disparity increased the risk of acute and chronic GVHD after unrelated donor (URD) transplantations compared to alloHSCT from HLA-matched sibling donors. Pharmacologic methods of immunosuppression that successfully prevent acute GVHD (aGVHD) are not equally effective in preventing cGVHD, underscoring the need for a better understanding and management of cGVHD.

It has been postulated that donor-derived alloreactive T cells play a role in the pathogenesis of both aGVHD and cGVHD. In cohort studies or retrospective registry analyses, ex vivo T-cell depletion (TCD) of the donor bone marrow or in vivo administration of antilymphocyte antibodies consistently reduced aGVHD but not always cGVHD.[36, 37] Since donor T cells also play a key role in mediating graft-versus-leukemia (GVL) effects, aggressive GVHD prevention strategies in patients with malignant disease may compromise beneficial antineoplastic GVT effects [10, 12]. Therefore, National Institutes of Health initiated a prospective, randomized multicenter trial to evaluate the impact of ex vivo TCD of marrow compared with unmodified grafts on disease-free survival in recipients of URD bone marrow transplants [26]. The focus of this report is to examine the effect of TCD, marrow cell doses, and other prognostic factors on the development of cGVHD and to describe clinical manifestations and outcomes in patients who develop cGVHD. Since no prospective studies have addressed risk factors associated with cGVHD in general, or specifically in URD marrow transplantation at a time, factors predicting survival after cGVHD were also investigated. Techniques were developed to remove donor T cells from the marrow graft (TCD), but randomized trials were lacking to prove the superiority of this strategy over conventional pharmacologically-based GVHD prevention with methotrexate and cyclosporine (M/C).

The incidence of cGVHD at two years was similar between the TCD and M/C arms, 29% versus 34% ($P=0.270$), respectively (**Figures 7 and 8**). Survival at three years from diagnosis of cGVHD was also similar, (TCD 51% versus M/C 58%; $P=0.290$). The proportion of patients with cGVHD who discontinued systemic immunosuppression at five years was not different (TCD 72% versus M/C 63%; $P=.27$). Incidence of leukemia relapse were similar on both treatment arms. For all patients at three years, the malignancy relapse rate was 24% (95% CI, 18%-29%) for TCD patients and 16% (95% CI, 11%-20%) for M/C patients ($P=0.08$). Patients who developed cGVHD had a significantly lower relapse probability within the TCD (28% versus 12%, $P=0.01$) and M/C (22% versus 4%, $P=0.01$) treatment arms. In a multivariate Cox proportional hazards model, significant and independently favorable risk factors for decreased risk of cGVHD are younger recipient age ($P=0.01$), higher infused CD34+ marrow dose ($P=0.01$), and prior acute GVHD of the grade of 0 or I ($P=0.01$), (**Table 1**). Among patients surviving 100 days after transplantation, 81% of patients with cGVHD had a serious (severe, life-threatening, or fatal) infection compared to 50% of patients who did not develop cGVHD ($P=0.01$). Multivariate analysis (**Table 2**; stratified on treatment arm) demonstrated that higher ($\geq 80\%$) Karnofsky-Lansky performance status ($P=0.01$), prior aGVHD grade 0-I ($P=0.03$), and HLA 6 of 6 match ($P=0.03$) each favorably influenced overall survival in patients with cGVHD. The prognostic factors were the same in both arms [26].

This study is the first randomized trial in unrelated donor transplants, which demonstrated for the first-time feasibility of conducting such trials in a multi-center setting. The results have shown that despite a significant reduction of acute GVHD, TCD did not reduce the incidence of cGVHD or improve survival in patients who developed cGVHD. The mean number of T cells infused was 1 log lower on the TCD arm which might not have been sufficient for reducing cGVHD. The implications of these findings provided the foundation for the future research of TCD of marrow or blood grafts as a method for GVHD prevention and determination of optimal CD3 cell doses. The current study also confirms the protective effect of cGVHD in the prevention of relapse. An average 1log TCD of the bone marrow does not abrogate this cGVHD-associated antineoplastic effect. Serious infections were more frequent in patients with cGVHD and were a major contributing cause of morbidity and mortality but the net adverse

effect of cGVHD and its therapy were largely independent of the initial randomized treatment. The exact mechanism of immune compromise due to cGVHD or treatment requires further research and new techniques to limit immune compromise.

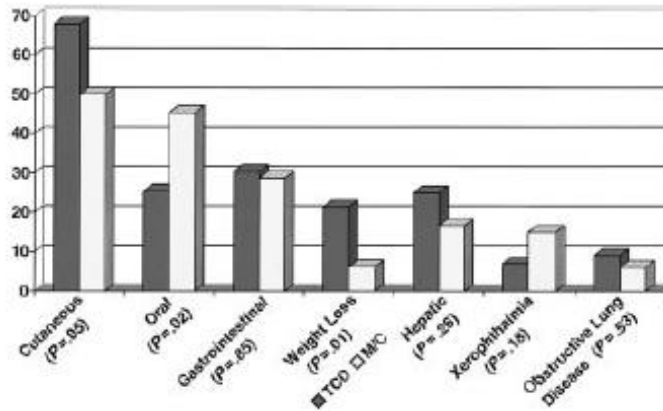


Figure 7. Chronic GVHD clinical manifestations at time of diagnosis.

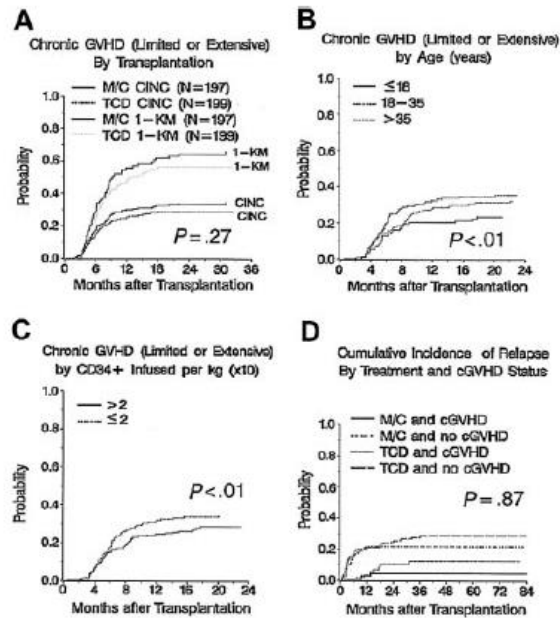


Figure 8. Cumulative incidence of chronic GVHD and relapse by covariates. (A) Cumulative incidence of chronic GVHD by treatment arm, $P = 0.27$. (B) Incidence of chronic GVHD by recipient age, $P = 0.01$. (C) Incidence of chronic GVHD by CD34+ dose, $P = 0.01$. (D) Cumulative incidence of relapse by treatment arm and chronic GVHD status, $P = 0.87$.

Table 1. Prognostic factors for developing cGVHD

			All patients, N = 404		
Development of cGVHD	CINC of cGVHD at 2 years	95% CI	Hazard ratio*	<i>P</i>	Favorable factors
Treatment arm					
M/C	0.34	0.27-0.40	1.22	.27	NA
TCD	0.29	0.22-0.35	1.00	NA	NA
Acute GVHD grade†					No prior aGVHD (0-I)
II-IV	NA	NA	1.84	< .01	NA
0-I	NA	NA	1.00	NA	NA
Recipient age					Younger recipients
Less than 19 years	0.23	0.14-0.32	1.00	NA	NA
18-35 years	0.35	0.27-0.43	2.51	< .01	NA
Greater than 35 years	0.32	0.25-0.40	2.44	< .01	NA
Primary disease					Diseases other than CML
CML	0.40	0.33-0.48	1.75	< .01	NA
Other	0.23	0.18-0.29	1.00	NA	NA
CD34⁺, infused/kg (x 10⁶)					Higher CD34 ⁺ infused
Less than or equal to 2.0	0.34	0.27-0.41	1.73	< .01	NA
Greater than 2.0	0.28	0.22-0.35	1.00	NA	NA

Variables that were considered and found not significant were date of transplantation, center, Karnofsky-Lansky performance status, sex of recipient and donor, donor age, HLA match, risk status, recipient and donor CMV status, recipient and donor race, method of T-cell depletion, T cells infused/kg, and total nucleated cell dose infused/kg.

NA indicates not applicable.

*Cox proportional hazards univariate analysis.

†Point estimates for aGVHD are not presented since it is a time-varying covariate.

Table 2. Final multivariate analysis: survival from cGVHD diagnosis

Survival Favorable factors	Hazard ratio	95% CI	P
Performance status at diagnosis			
Less than 80	2.67	1.54-4.60	.01
Performance status of 80-100 Greater than or equal to 80		1.00	NA
Acute GVHD grade			
Acute GVHD grade 0 or I			
II, III, or IV	1.99	1.09-3.63	.03
0 or I	1.00	NA	NA
HLA match			
6 of 6 HLA match			
5 of 6	1.92	1.05-3.57	.03
6 of 6	1.00	NA	NA

Stratified on treatment because of nonproportional hazards. NA indicates not applicable.

4.2. Paper 2

By the early 2000s, most alloH SCT were performed by using G-CSF mobilized peripheral blood (alloPBSCT) instead of the bone marrow as the preferred source of hematopoietic stem cells. PBSCTs resulted in more rapid engraftment, shorter hospital stays and no need for general anesthesia exposure of the donor. However, such grafts have resulted in higher incidence of cGVHD as compared to bone marrow grafts, albeit no survival difference in randomized trials was shown when BMT vs. BSCT was compared. One of the serious obstacles to progress in cGVHD clinical studies at the time was the lack of accepted staging and response criteria. Two new cGVHD prognostic systems have been proposed based on one large registry-based analysis and one single-institution analysis.[38, 39] Both prognostic systems were formulated from clinical observations of patients who almost exclusively received an allogeneic bone marrow transplant (alloBMT). Peripheral blood grafts are biologically and by cell composition substantially different than bone marrow grafts, including 2 log higher number of T cells, up to 1 log more of CD34+ hematopoietic progenitors and skewed Th1/Th2 cell polarization. However, it was unknown if these biological differences could potentially result in different prognostic factors for the onset and outcomes of cGVHD. This study was the first to address this question in a retrospective comparison design.

The clinical characteristics of transplanted patients are presented in **Table 3**. Factors significantly associated with a higher incidence of cGVHD after alloPBSCT included CMV-positive donor, acute skin GVHD, and diagnoses other than lymphoma (**Table 4**). Factors predictive for poor survival following cGVHD diagnosis included platelet count $< 100,000/\text{mm}^3$ and a history of acute liver GVHD (**Figure 9**). Acute liver GVHD and etoposide in the preparative regimen significantly increased the risk of death due to cGVHD after alloPBSCT. All alloPBSCT multivariate models were fit to an independent cohort of comparable matched related donor alloBMT patients ($n = 75$). After alloBMT, only acute skin GVHD and diagnoses other than lymphoma retained prognostic significance for predicting cGVHD. Low platelet count was the only variable predictive for poor survival in cGVHD patients after alloBMT. Acute liver GVHD was the only factor that retained prognostic significance for risk of death due to cGVHD

after alloBMT. These data suggest there are some cGVHD prognostic factors that may be unique to recipients of alloPBSCT. This study provided an impetus for future in depths studies of factors which determine chronic GVHD biology and differential clinical outcomes depending on the hematopoietic stem cell (blood vs. marrow) product. In summary, this study for the first time, identified several independent prognostic factors of cGVHD incidence and severity in a group of patients that all received alloPBSCT stem cells. Some of the prognostic factors identified in alloPBSCT patients may not be applicable to the alloBMT recipients. This paper provided an impetus for more studies to develop better cGVHD prognostic systems and whether they may be used interchangeably in patients receiving different stem-cell products.

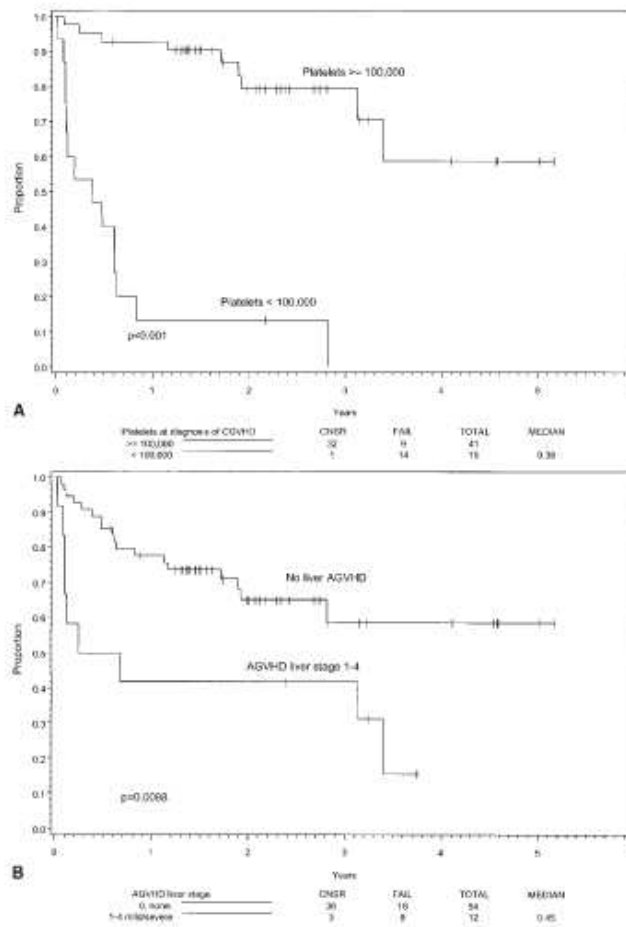


Figure 9. Survival following chronic GVHD after allogeneic blood stem-cell transplantation according to prognostic factors identified in the multivariate analysis. Only patients who developed cGVHD are included (n = 66). (A) Patients with more versus less than 100,000/mm³ platelets at cGVHD diagnosis. (B) Patients without prior history of acute GVHD of the liver versus those with prior acute liver GVHD.

Table 3. Clinical Characteristics of Transplanted Patients

	AlloPBSCT (<i>n</i> = 87)	AlloBMT (<i>n</i> = 75)	<i>P</i>
Median age in years at transplant (range)	40 (20–60)	37 (17–60)	0.0026
Female: <i>n</i> (%)	38 (44%)	37 (49%)	0.53
White, non-Hispanic: <i>n</i> (%)	83 (95%)	73 (97%)	0.69
Disease: <i>n</i> (%)			
Leukemia/MDS	54 (62%)	59 (79%)	0.067
Lymphoma	28 (32%)	14 (19%)	
Multiple Myeloma	5 (6%)	2 (3%)	
High relapse risk: <i>n</i> (%) ^a	46 (53%)	36 (48%)	0.64
CMV-negative recipient: <i>n</i> (%)	42 (48%)	44 (59%)	0.21
HSV-negative recipient: <i>n</i> (%)	18 (22%)	19 (29%)	0.35
Etoposide: <i>n</i> (%)	18 (21%)	69 (92%)	<0.0001
TBI: <i>n</i> (%)	81 (93%)	67 (89%)	0.42
History of smoking: <i>n</i> (%)	53 (62%)	59 (80%)	0.023
Median age in years of donor (range)	42 (18–73)	37 (6–62)	0.0043
Female donor: <i>n</i> (%)	42 (48%)	32 (43%)	0.53
CMV-negative donor: <i>n</i> (%)	42 (49%)	34 (46%)	0.75
Days to 500 neutrophils (range)	12 (9–23)	18 (10–73)	<0.001
Days to 500 lymphocytes (range)	19 (9–228)	41 (10–475)	<0.001
Median CD34 dose/kg (10 ⁶) (range)	8.12 (1.77–37.9)	N	—
Median CD3 dose/kg (10 ⁸) (range)	5.97 (1.73–12.76)	N	—
Median MNC dose/kg (10 ⁸) (range)	9.08 (2.95–16.84)	N	—
<4 MTX number of doses (%)	14 (17%)	16 (38%)	0.014
Missing	5	33	
<100 K Platelets at day 100 (%)	18 (23%)	10 (20%)	0.83
Missing	5	33	
Prior AGVHD grade: <i>n</i> (%)			
0	23 (26%)	24 (32%)	0.10
I	13 (15%)	17 (23%)	
II	33 (38%)	23 (31%)	
III	12 (14%)	11 (15%)	
IV	6 (7%)	0 (0%)	
AGVHD GI stage: <i>n</i> (%)			
0 ¼ none	58 (67%)	52 (69%)	0.74
1–4 ¼ mild/severe	29 (33%)	23 (31%)	
AGVHD liver stage: <i>n</i> (%)			
0 ¼ none	71 (82%)	61 (82%)	1.00
1–4 ¼ mild/severe	16 (18%)	13 (18%)	
AGVHD skin stage: <i>n</i> (%)			
0 ¼ none	39 (45%)	28 (37%)	0.34
1–4 ¼ mild/severe	48 (55%)	47 (63%)	
AGVHD upper GI stage: <i>n</i> (%)			
0 ¼ none	23 (26%)	24 (32%)	0.49
1–4 ¼ mild/severe	64 (74%)	51 (68%)	

^aPatients at low risk of malignancy relapse were those with acute leukemia in first remission, chronic myelogenous leukemia in first chronic phase, myelodysplastic syndromes without increased blasts, and lymphoma or chronic lymphocytic leukemia in remission or untreated first relapse

Table 4. Chronic Graft-Versus-Host Disease Prognostic Factors After Allogeneic Blood Stem-Cell Transplantation Identified in the Multivariate Analysis and Applied to the Independent Cohort of Allogeneic Bone Marrow Transplantation Patients*

(a) Factors predicting cGVHD after transplantation				
Risk factor	AlloPBSCT (<i>n</i> ¼ 87)		AlloBMT (<i>n</i> ¼ 75)	
	RR (95% CI)	<i>P</i> value	RR (95% CI)	<i>P</i> value
CMV+ donor ^a	2.5 (1.4–4.4)	0.0017	1.1 (0.5–2.6)	0.82
Acute GVHD, skin	2.0 (1.1–3.7)	0.018	4.8 (1.7–13.2)	0.0026
Lymphoma	0.5 (0.3–0.9)	0.022	0.1 (0.0–0.8)	0.028
(b) Factors predicting overall survival after cGVHD diagnosis				
Risk factor	AlloPBSCT (<i>n</i> ¼ 66)		AlloBMT (<i>n</i> ¼ 47)	
	RR (95% CI)	<i>P</i> value	RR (95% CI)	<i>P</i> value
Platelets < 100 K	25.9 (5.7–118.4)	<0.000	3.0 (1.3–7.0)	0.010
Acute GVHD, liver ^a	12.0 (2.8–52.0)	0.0009	1.7 (0.6–4.5)	0.29
(c) Factors predicting cGVHD-specific mortality after transplantation				
Risk factor	AlloPBSCT (<i>n</i> ¼ 87)		AlloBMT (<i>n</i> ¼ 75)	
	RR (95% CI)	<i>P</i> value	RR (95% CI)	<i>P</i> value
Acute GVHD, liver	3.3 (1.2–8.9)	0.017	2.9 (1.0–8.3)	0.044
Etoposide ^a	2.9 (1.1–7.3)	0.029	1.4 (0.2–10.5)	0.76

*Abbreviations: MTX, methotrexate; CMV, cytomegalovirus; RR, relative risk.

^aprognostic factors significant after alloPBSCT but not after alloBMT.

4.3. Paper 3

The lack of standardized criteria for quantitative measurement of therapeutic response in clinical trials posed a major obstacle for the development of new therapeutic agents in cGVHD. This 2005 NIH consensus project document was developed to address several objectives for response criteria to be used in cGVHD-related clinical trials. Because no available databases had information from patients with cGVHD at a sufficient level of detail, retrospective methods could not be used to identify clinical characteristics that are sensitive to change and predictive for major outcomes.

Overall survival or survival to permanent resolution of GVHD and discontinuation of systemic immunosuppression are long-term clinical outcomes that have been accepted major end

points in cGVHD clinical trials, but these long-term outcomes are not suitable for early phase therapy studies. Qualitative assessments of cGVHD manifestations can guide clinical decisions but are not adequate for reliable measuring outcomes in clinical trials. To accelerate development of novel therapeutic agents in cGVHD, quantitative standard research tools are needed to measure short-term responses. This paper provided an impactful paradigm shifting set of recommendations and tool that changed and propelled the field of cGVHD clinical research.

Here are outlined the key recommendations put forward by the 2005 NIH cGVHD Consensus Project Response Criteria:

1. Proposed chronic GVHD-specific core measures include:

- A. Clinician- or patient-assessed signs and symptoms.
- B. The cGVHD symptom scale by Lee et al [40]
- C. The clinician- or patient-reported global rating scales (**Table 5**).

To facilitate validation studies, continuous data should be recorded as such and should not be reduced to prespecified categories.

2. Proposed cGVHD nonspecific ancillary measures for adults include:

- A. Measurement of grip strength and 2-minute walk time.
- B. Patient-reported Human Activity Profile (HAP) questionnaire [41]
- C. Clinician-assessed Karnofsky performance status.
- D. The SF-36 version 2 questionnaire and FACT-BMT for quality-of-life assessments (**Table 6**) [42] [43]

The ancillary cGVHD nonspecific measures are optional and should not be used as primary end points in chronic GVHD trials.

3. Age-appropriate modifications of existing measures should be used and explored in children with chronic GVHD.

4. Definition of response involves a comparison of chronic GVHD activity at two different time points. Provisional definitions of complete response, partial response, and progression are offered for each organ and for overall outcomes. Simple forms to be used for clinician and patient assessments are provided (Forms A and B in the original paper appendices).[18] In each specific trial, irreversible baseline organ damage may be defined initially and then excluded

in response assessments.

5. Measures should be made at 3-month intervals and whenever a major change is made in treatment. Permanent discontinuation of systemic immunosuppressive treatment indicates a durable response.

6. Further assistance from subspecialists will be needed to develop organ- or site-specific measures that could improve the sensitivity of cGVHD assessments. Specific organ or site assessments discussed by the Working Group include the following:

A. Skin: skin-specific scoring systems, durometer, biopsy, or imaging (ultrasound, magnetic resonance imaging)

B. Eyes: corneal staining grading, conjunctival grading, ocular surface disease index.

C. Oral: Oral Mucositis Rating Scale.

D. Vulvar-vaginal: organ-specific staging.

E. Function: range of motion, limb volume, fatigue severity scale.

Subsequent decade brought the validation of these concepts through many prospective observation studies in the USA and Europe which resulted in this time evidence based, 2014 revised NIH cGVHD response criteria which served as foundation for trials which led to first ever FDA approvals of an agent for cGVHD indication (ibrutinib in 2017, belumosudil and ruxolitinib in 2021 [23, 44].

Table 5. 2005 NIH Criteria Proposed Measures for Assessing Responses in Chronic GVHD Trials

Measure	Clinician Assessed	Patient Reported
I. Chronic GVHD-specific core measures		
Signs	Organ-specific measures	N/A
Symptoms	Clinician-assessed symptoms	Patient-reported Lee symptom scale [12]
Global rating	Mild-moderate-severe [12] 0-10 severity scale [13] 7-point change scale [14]	Mild-moderate-severe [12] 0-10 severity scale [13] 7-point change scale [14]
II. Chronic GVHD-nonspecific ancillary measures		
Function	Grip strength [15-17] 2-min walk time [18]	HAP [19] ASK in children [23-25]
Performance status	Karnofsky or Lansky [26]	
Quality of life		SF-36v.2 [20,21] or FACT-BMT [22] in adults, CHRIs [27-29]

ASK indicates Activities Scale for Kids; GVHD, graft-versus-host disease; N/A, not applicable; HAP, Human Activity Profile; CHRIS, Child Health Ratings Inventories

Table 6. 2005 Proposed Clinician-Assessed and Patient-Reported Chronic GVHD-Specific Measures

Component	Items Assessed	Measure	Assessor
Skin	Erythematous rash of any sort	% Body surface area	C
	Movable sclerosis	0%-100% For each feature	C
	Nonmoveable sclerosis or subcutaneous sclerosis/fasciitis	By using rule of nines	C
	Ulcers	Largest dimension (cm) of the largest ulcer	C
Eyes	Pruritus or itching	0-10 Scale	P
	Bilateral Schirmer's tear test scores without anesthesia	Mean of both eyes, mm	C
Mouth	Main ocular symptom at the time of the visit	0-10 Scale	P
	Erythema	Total score 0-15	C
Hematology	Lichen-type hyperkeratosis		C
	Ulcerations		C
	Mucoceles		C
	Symptoms of oral pain, dryness, sensitivity	0-10 Scale	P
GI	Platelet count	Number/ μ L	C
	Eosinophils	Percent	C
Liver	Upper GI symptoms	0-3 Score	C
	Esophageal symptoms	0-3 Score	C
	Diarrhea	0-3 Score	C
Lungs	Total serum bilirubin	mg/dL	C
	ALT, alkaline phosphatase	U/L	C
Chronic GVHD symptom scale [12]	Bronchiolitis obliterans syndrome	FEV ₁ , DLCO	C
	30 items, 7 subscales, 1 summary scale	0-100	P
Global activity rating	Severity of chronic GVHD symptoms	0-10	C/P
	Perception of change	+3 to -3	C/P
	Overall severity of chronic GVHD	Mild – moderate-severe	C/P

ALT indicate alanine aminotransferase; C, assessed by the clinician; DLCO, diffusion lung capacity for carbon monoxide; FEV₁, forced expiratory volume in the first second; GI, gastrointestinal; GVHD, graft-versus-host disease; P, reported by the patient.

Vulvar-vaginal symptoms (yes or no) and patient weight should be recorded at each visit.

Range of motion of the most affected joints should be recorded depending on the availability of a physical therapist.



Figure 10. Skin manifestations for response to chronic GVHD. A erythematous papular rash, B erythematous rash with papules and small scaly plaques, C dermal sclerosis and D subcutaneous sclerosis

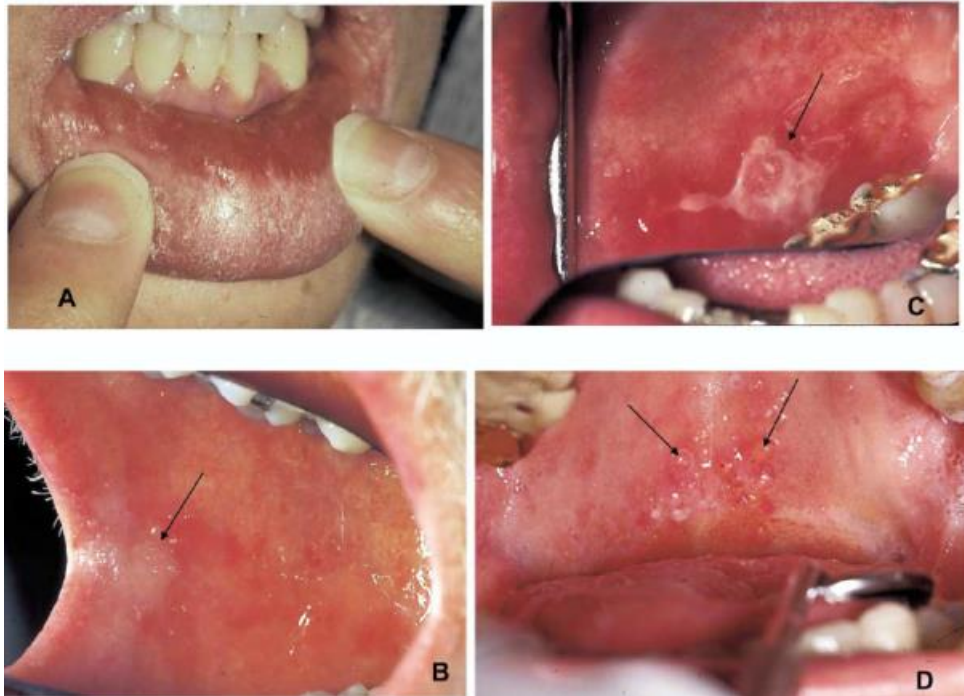


Figure 11. Oral manifestatiосn of GVHD. A moderate erythema, B sheet-like lichenoid hyperkeratosis, C ulcer with pseudomembranous fibrin exudates, and D mucoceles at the palate centre

4.4. Paper 4

After first FDA approvals of new therapies for cGVHD in 2017 and 2021 the field has now begun to develop novel targeted agents for treatment of chronic GVHD. The scope of the disease and its clinical course are now much more thoroughly characterized, and its complex pathophysiology is better understood than in 2005 [14]. An increasing number of investigational agents are now available for treatment, and resources are now available thanks to greater industry and government funding. This momentum has also led to development of the first US-based National Comprehensive Cancer Network guideline for GVHD management [45]. Although the survival of patients with the most severe forms of chronic GVHD has likely improved due to better supportive care, the algorithm for the selection of appropriate systemic therapy has still not changed since the 1980s. Namely initial treatment still relies on prednisone with or without a calcineurin inhibitor, which does not control the disease in most patients, and trial and error are the strategy for subsequent treatment choices. We have no guide for patient-tailored approaches for prevention or preemption, and highly morbid disabling forms of chronic GVHD still occur all too frequently. Our goal to eliminate chronic GVHD as a source of patient suffering while improving long term outcomes after allogeneic HCT remains elusive, although we now have the tools to achieve these objectives. In contrast to the 2005 and 2014 NIH consensus conferences, the main goal of the 2020 project was not to standardize or revise clinical research tools already developed but rather to stimulate the field by identifying basic and clinical research directions that may lead to fundamental change in cGVHD management over following 3 to 7 years (**Figure 12**).

Working group 1 was tasked with addressing gaps in knowledge about the donor and recipient etiologic processes that occur early after HCT to initiate cGVHD. The concept of “second hits,” such as viral infections and acute GVHD, is introduced that may further incite the pathogenesis of cGVHD. “Prevention” is strictly defined as an intervention applied based on cGVHD risk information known before transplant, regardless of when the intervention is given. Well-established prevention strategies such as T cell depletion or post-transplant high-dose cyclophosphamide are being tested. The main downside of prevention is that the intervention is

given to all subjects regardless of whether they are destined to develop chronic GVHD. Accordingly, we have a major unmet need to develop accurate risk-stratification systems to be utilized before or at the time of HCT that would allow personalized approaches for assigning specific chronic GVHD preventive interventions for individual patients.

Working group 2 was tasked with proposing strategies for the development of preemptive approaches to cGVHD. “Preemption” is defined as an intervention applied after HCT prompted by secondary events, signs, symptoms, or biomarkers indicating that the risk of cGVHD in a patient is higher than had been previously appreciated. Preemptive treatment may be the optimal approach because people who have a high risk of chronic GVHD are treated early before the onset of manifest disease. Clinical trials are needed to determine whether such early intervention would lower the incidence of moderate to severe chronic GVHD and improve long-term outcomes. Early signs and symptoms of chronic GVHD that are reliably associated with later progression to highly morbid forms of cGVHD must be identified. Earlier clinical recognition of cGVHD will require greater involvement of non-transplant providers, as well as patients and caregivers, and could be facilitated by technology such as telehealth, teleconferences, and electronic reporting tools.

Working group 3 was tasked with recommending ways to improve systemic treatment for cGVHD. Development of effective regimens that reduce or eliminate the need for concurrent corticosteroid treatment is a high priority. Even with best modern therapies for steroid-refractory chronic GVHD, complete response rates are typically <10%, and the disease eventually recurs or progresses in 50% to 70% of patients. The field should move from the current empirical trial-and-error approach to treatment after failure of corticosteroids toward biology-based prognostic algorithms that guide a personalized treatment approach based on selection of specific agents according to clinical and biological profile. Ultimately, it might be possible to develop adaptive platform protocols that enable rapid clinical screening of new agents in early-phase studies, although new organizational structures will be needed to conduct such trials and simultaneously manage the interests of multiple stakeholders [46].

Working group 4 reviewed highly morbid forms of cGVHD, such as lung, skin sclerosis, intestinal tract, and eye involvement that pose special challenges due to their disabling and recalcitrant nature. Such patients carry the greatest burden of chronic GVHD symptoms, functional disability, psychosocial dysfunction, and impairments in quality of life. Better understanding of fibrosis in chronic GVHD biology has identified several promising novel targets and combination approaches to be tested. High priorities include the establishment of primary endpoints appropriate for each highly morbid manifestation and the need for novel trial designs that can be informative after enrolling small numbers of patients.

All the working groups identified development of qualified biomarkers for clinical use as an overarching prominent unmet need. Adhering to standard terminology and guidelines for clinical development and verification of top candidates is imperative. Although a number of potential candidate biomarkers in cGVHD have been identified, their clinical development has lagged behind similar efforts in acute GVHD for a variety of reasons, including complex clinical presentation, long time trajectory, and lack of standardization in clinical studies and sample processing. Definitions from the Food and Drug Administration's Biomarkers, EndpointS, and other Tools (BEST) Resource, and the prior NIH conference guidelines should be used to integrate biomarkers into chronic GVHD drug development [22].

The expectation is that the new concepts put forward by the 2020 NIH Consensus Conference will result in fundamentally new approaches, personalized and more effective treatments and prevention of cGVHD during the next decade. Pathways to achieving this goal defined by this paper have been recently published in *Blood Advances* [47].


Chronic GVHD Four Working Groups – 2020 NIH Consensus Framework			
			
Intervention based on pre-transplant characteristics	Intervention based on post-transplant information	Established chronic GVHD per NIH criteria	Severe, advanced chronic GVHD
WG1	WG2	WG3	WG4
Etiology/Prevention	Diagnosis/Preemptive therapy	Systemic treatment	Highly morbid manifestations
Understanding of biologic processes/ Interventions applied based on chronic GVHD risk known before transplant, regardless of when the intervention is given	Early diagnosis/ Interventions applied after transplant based on a higher than previously appreciated risk of developing chronic GVHD based on secondary events, signs, symptoms, or biomarkers	Systemic treatments for established chronic GVHD, including initial and subsequent therapies	Understanding of the biologic differences in highly morbid chronic GVHD manifestations/ local and systemic interventions specifically targeting these morbid conditions

Figure 12. 2020 NIH Consensus Development Project on Criteria for Clinical Trials in Chronic GVHD working groups and their scopes.

5. COPIES OF THE POOLED PAPERS

1. **Pavletic, S.Z.**, Carter, S.L., Kernan, N.A., Henslee-Downey, J., Mendizabal, A.M., Papadopoulos, E., Gingrich, R., Casper, J., Yanovich, S., Weisdorf, D., National Heart, Lung and Blood Institute Unrelated Donor Marrow Transplantation, T., Influence of T-cell depletion on chronic graft-versus-host disease: results of a multicenter randomized trial in unrelated marrow donor transplantation Blood 106: 3308-3313, 2005.
2. **Pavletic, S.Z.**, Smith, L.M., Bishop, M.R., Lynch, J.C., Tarantolo, S.R., Vose, J.M., Bierman, P.J., Hadi, A., Armitage, J.O. and Kessinger, A., Prognostic factors of chronic graft-versus-host disease after allogeneic blood stem-cell transplantation Am J Hematol 78: 265-274, 2005.
3. **Pavletic, S.Z.**, Martin, P., Lee, S.J., Mitchell, S., Jacobsohn, D., Cowen, E.W., Turner, M.L., Akpek, G., Gilman, A., McDonald, G., Schubert, M., Berger, A., Bross, P., Chien, J.W., Couriel, D., Dunn, J.P., Fall-Dickson, J., Farrell, A., Flowers, M.E., Greinix, H., Hirschfeld, S., Gerber, L., Kim, S., Knobler, R., Lachenbruch, P.A., Miller, F.W., Mittleman, B., Papadopoulos, E., Parsons, S.K., Przepiorka, D., Robinson, M., Ward, M., Reeve, B., Rider, L.G., Shulman, H., Schultz, K.R., Weisdorf, D. and Vogelsang, G.B., 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 12: 252-266, 2006.
4. **Pavletic SZ**, Martin PJ, Schultz KR, Lee SJ. The Future of Chronic Graft-Versus-Host Disease: Introduction to the 2020 National Institutes of Health Consensus Development Project Reports. Transplant Cell Ther. (Former Biol Blood Marrow Transplant) 2021 Mar 2:S2666-6367(21)00741-7. doi: 10.1016/j.jtct.2021.02.034. Epub ahead of print. PMID: 33785366.

Influence of T-cell depletion on chronic graft-versus-host disease: results of a multicenter randomized trial in unrelated marrow donor transplantation

Steven Z. Pavletic, Shelly L. Carter, Nancy A. Kernan, Jean Henslee-Downey, Adam M. Mendizabal, Esperanza Papadopoulos, Roger Gingrich, James Casper, Saul Yanovich, and Daniel Weisdorf, for the members of the National Heart, Lung, and Blood Institute Unrelated Donor Marrow Transplantation Trial

Donor-derived T cells have been proposed to play a role in pathogenesis of chronic graft-versus-host disease (cGVHD). The impact of ex vivo T-cell depletion (TCD) on cGVHD was analyzed in a randomized multicenter trial involving unrelated donor marrow transplants. A total of 404 patients diagnosed with hematologic malignancies received a total body irradiation–based myeloablative conditioning regimen. GVHD prophylaxis included TCD plus cyclosporine (CSA) or

unmodified grafts with CSA plus methotrexate (M/C). Median recipient age was 31.2 years (range, 0.5-55.6 years); median follow-up time since randomization was 4.2 years. The mean number of T cells infused was 1 log lower on the TCD arm. The incidence of cGVHD at 2 years was similar between the TCD and M/C arms, 29% versus 34% ($P = .27$), respectively. Survival at 3 years from diagnosis of cGVHD was also similar, (TCD 51% versus M/C 58%; $P = .29$). The proportion of

patients with cGVHD who discontinued immunosuppression at 5 years was not different (TCD 72% versus M/C 63%; $P = .27$), and incidence of serious infections and leukemia relapse were similar on both treatment arms. In spite of a significant reduction of acute GVHD, TCD did not reduce the incidence of cGVHD or improve survival in patients who developed cGVHD. (Blood. 2005;106:3308-3313)

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Introduction

Chronic graft-versus-host disease (cGVHD) is a multiorgan system immune disorder that is a major complication after allogeneic hematopoietic stem cell transplantation (HSCT).¹ Chronic GVHD is also a leading cause of ongoing posttransplantation morbidity and mortality.^{2,3} Each year about 7000 patients undergo HSCT in North America for the treatment of malignant or nonmalignant diseases.⁴ In patients surviving at least 100 days, approximately 50% develop cGVHD. Due to greater donor recipient genetic disparity, the risk of acute and chronic GVHD is increased after unrelated donor (URD) transplantations when compared with HSCTs from HLA-matched sibling donors.⁵⁻⁸ Pharmacologic methods of immunosuppression that successfully prevent acute GVHD (aGVHD) are not equally effective in preventing cGVHD, underscoring the need for better understanding and management of cGVHD.⁹⁻¹¹ It has been postulated that donor-derived alloreactive T cells play a role in the pathogenesis of both aGVHD and cGVHD.¹² In cohort studies or retrospective registry analyses, ex vivo T-cell depletion (TCD) of the donor bone marrow or in vivo administration of antilymphocyte antibodies consistently reduces aGVHD, but not always cGVHD.^{6,13-16} Since donor T cells also play a key role in mediating graft-versus-tumor (GVT) effects, aggressive GVHD prevention strategies in patients with malignant disease may compromise beneficial antineoplastic GVT effects.^{17,18}

In 1995, the National Heart, Lung, and Blood Institute initiated a prospective, randomized multicenter trial to evaluate the impact of ex vivo TCD of marrow as compared with unmodified grafts on disease-free survival in recipients of URD bone marrow transplants.¹⁹ The focus of this report is to examine the effect of TCD, marrow cell doses, and other prognostic factors on the development of cGVHD and to describe clinical manifestations and outcomes in patients who develop cGVHD. Since no prospective studies have addressed risk factors associated with cGVHD in general, or specifically in URD marrow transplantation, factors predicting survival after cGVHD are also presented.

Patients, materials, and methods

Patients and donors

The Unrelated Donor Marrow Transplantation Trial included 15 participating transplantation centers. Between March 1995 and October 2000, 410 patients with hematologic malignancies were randomized; 203 patients were randomized to receive T-cell–depleted marrow and cyclosporine (TCD arm) and 207 to receive methotrexate and cyclosporine after transplantation of T-cell–replete marrow (M/C arm). The study protocol was approved by the institutional review boards (IRBs) at each transplantation center, and all patients signed IRB-approved consent forms prior to

From the University of Nebraska Medical Center, Omaha; The EMMES Corporation, Rockville, MD; Memorial Sloan-Kettering Cancer Center, New York, NY; University of South Carolina, Columbia; University of Iowa, Iowa City; Medical College of Wisconsin, Milwaukee; Medical College of Virginia, Richmond; University of Minnesota, Minneapolis.

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A complete list of the members of the National Heart, Lung, and Blood Institute Unrelated Donor Marrow Transplantation Trial appears in the "Appendix."

Reprints: Steven Pavletic, Graft-Versus-Host and Autoimmunity Unit, Experimental Transplantation and Immunology Branch, National Cancer Institute, Bldg 10, Rm CRC 3-3330, Bethesda, MD, 20892-1907; e-mail: pavletis@mail.nih.gov.

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initiation of treatment. Of the 410 patients randomized, 5 died before undergoing transplantation (TCD, $n = 2$; M/C, $n = 3$) and one patient underwent transplantation 2 years later. Median recipient age was 31.2 years (range, 0.5-55.6 years). Diagnoses included chronic myelogenous leukemias (CML; $n = 182$), acute myelocytic leukemia (AML; $n = 103$), acute lymphocytic leukemia (ALL; $n = 88$), myelodysplastic syndrome (MDS; $n = 23$), non-Hodgkin lymphoma (NHL; $n = 3$), and other leukemia ($n = 11$). The mean infused CD3⁺ cell doses were 2.8 ± 12.9 (standard deviation [SD]) $\times 10^6/\text{kg}$ and $30.1 \pm 22.0 \times 10^6/\text{kg}$ in the TCD and M/C arms, respectively. The mean infused CD34⁺ cell doses were $2.0 \pm 1.8 \times 10^6/\text{kg}$ and $3.8 \pm 3.4 \times 10^6/\text{kg}$ in the TCD and M/C arms, respectively. The protocol required donors to be selected based on matching of HLA-A and -B determined by serologic level typing and HLA-DRB1 determined by high-resolution molecular typing. Overall, 298 (73%) patients received an HLA 6 of 6 match. In patients with an HLA 5 of 6 match, 10% were mismatched at HLA-A ($n = 40$), 9% at HLA-B ($n = 36$), and 9% at HLA-DRB1 ($n = 36$). The median donor age was 36 years (range, 19-59 years); 61% of donors were male.¹⁹

Transplantation procedures

Two methods of TCD were employed: counterflow centrifugal elutriation (Beckman, Palo Alto, CA), a physical method of separating T cells from hematopoietic stem and progenitor cells, and T10B9 (MEDI-500; Medimmune, Gaithersburg, MD), an antibody method of targeting the $\alpha\beta$ subunit of the T-cell receptor, which lyses bound cells in the presence of rabbit complement.^{20,21}

Because conditioning regimen varied by type of GVHD prophylaxis, the study evaluated the treatment package. Recipients of TCD received additional therapy in order to promote engraftment. Patients who received marrow T-cell depleted by T10B9 plus complement ($n = 134$) received conditioning consisting of 1410 cGy fractionated total body irradiation (TBI) over 3 days, 9 gm/m² cytarabine over 3 days, and 100 mg/kg cyclophosphamide over 2 days. Patients who received TCD by elutriation ($n = 67$) received a conditioning regimen consisting of 1320 cGy to 1375 cGy TBI over 4 days, 120 mg/kg cyclophosphamide over 2 days, and 60 mg/kg per day equine antithymocyte globulin over 2 days. Patients randomized to M/C received 1320 cGy to 1375 cGy fractionated TBI and 120 mg/kg cyclophosphamide over 2 days. For GVHD prophylaxis, all patients received cyclosporine after transplantation. Patients on the M/C arm also received intravenous methotrexate: 15 mg/m² on day 1 and 10 mg/m² on days 3, 6, and 11.¹⁰

Data collection

National Marrow Donor Program (NMDP) data forms were prospectively collected at baseline, 100 days, 6 months, 1 year, and annually thereafter along with supplemental data forms developed by the Medical Coordinating Center (The EMMES Corporation, Rockville, MD).

The data on each patient were reviewed (blinded to treatment arm) by expert panels to assign an aGVHD score,²² infection scores for types and severities of infection (Jo-Anne van Burik, S.L.C., Allison G. Freifeld, manuscript in preparation), and a cause of death defined by prespecified criteria. The occurrence of cGVHD was determined from the first report of cGVHD diagnosis on the NMDP forms. Subsequent queries were sent to the transplantation centers to obtain the dates of completion of systemic therapy for cGVHD.

Statistical analysis

The primary end point was the incidence of any stage (extensive or limited) cGVHD. To describe the actual risk of cGVHD at the time of transplantation, the complement of the Kaplan-Meier (1-KM) and the cumulative incidence estimate (CINC) for cGVHD were determined.²³ The 1-KM and the CINC are both marginal estimates of the probability of failure due to the event of interest but differ in the way they handle the competing risk of death, and have different interpretations. The 1-KM estimate is uniformly higher than the CINC because in the computation of 1-KM, patients who die early are censored and their probability of failing from the defined end

point is redistributed across later time points, whereas in the computation of the CINC estimate, these individuals are no longer at risk for the end point. The 1-KM predicts the cumulative probability of the end point in the absence of any competing risk. The CINC estimates the cumulative probability of the end point when the competing risk is present.^{23,24} Kaplan-Meier estimates were used to estimate survival,²⁵ and differences between groups were compared using the log-rank statistic.²⁶ The Cox proportional hazards model with time-dependent covariates was used to create prognostic models that considered multiple variables.²⁷ Variables considered were: treatment arm; TCD method; transplantation center; total CD3⁺, CD34⁺, and nucleated cell doses; recipient and donor demographics; primary disease; risk status; degree of HLA match; recipient and donor cytomegalovirus (CMV) serologic status; median days to neutrophil engraftment; previous maximum aGVHD grade; and organs involved. For the analyses of patients diagnosed with cGVHD, additional variables included Karnofsky-Lansky performance score, serum bilirubin level and platelet count at the time of diagnosis, and the organs involved. Incidence of relapse was estimated with death in remission as a competing risk. Time to termination of all systemic immunosuppression was estimated with death while receiving immunosuppression considered as a competing risk.

Results

Overall

With a median 4.2 years (range, 1.5-7.0 years) follow-up from date of randomization, the primary study end point, 3-year disease-free survival (DFS) was not statistically different between the TCD (27%; 95% confidence interval [CI], 21%-33%) and M/C (34%; 95% CI, 27%-40%) arms ($P = .16$). Overall survival for all randomized patients at 3 years after HSCT was also not significantly different between treatment arms (TCD: 34%; 95% CI, 27%-40%; M/C: 36%; 95% CI, 29%-43%). The proportion of patients experiencing infection, time to first infection, and types of infections were similar. Severity of infections (particularly CMV infections) was greater in TCD recipients (van Burik JH, Carter SL, Freifeld AG, et al, manuscript submitted 2005). Using the Bearman toxicity scale, the incidence and severity of mucositis, hepatic, pulmonary, renal, and central nervous system (CNS) toxicities were greater among recipients of M/C.¹⁹

Acute GVHD

The cumulative incidence estimates of acute GVHD grades II-IV at day 100 were significantly lower in the TCD arm than in the M/C arm, 39% (95% CI, 33%-46%) versus 63% (95% CI, 56%-69%), respectively ($P < .01$). Incidence of acute GVHD grades III-IV was also lower in the TCD arm, 18% (95% CI, 13%-24%) versus 37% (95% CI, 30%-44%), respectively ($P < .01$).

Incidence of chronic GVHD

Overall, 124 patients developed cGVHD (TCD = 57, M/C = 67). The median time of occurrence of cGVHD was 180 days (range, 64-943 days) after transplantation, with no difference in the median time of cGVHD onset between treatment arms (TCD, 181 days versus M/C, 179 days; $P = .71$). For all patients, the CINC of cGVHD at 2 years was 31% (95% CI, 27%-36%) and the 1-KM estimate was 61% (95% CI, 54%-68%). There was no statistically significant difference at 2 years in the cGVHD CINC estimates between treatment arms: 29% (95% CI, 22%-35%) in recipients with TCD and 34% (95% CI, 27%-40%) in recipients of M/C ($P = .27$). Similarly, there was no difference in the 1-KM estimates of cGVHD between TCD and M/C: 56% (95% CI, 46%-67%) versus 64% (95% CI, 55%-74%), respectively ($P = .27$; Figure 1A).

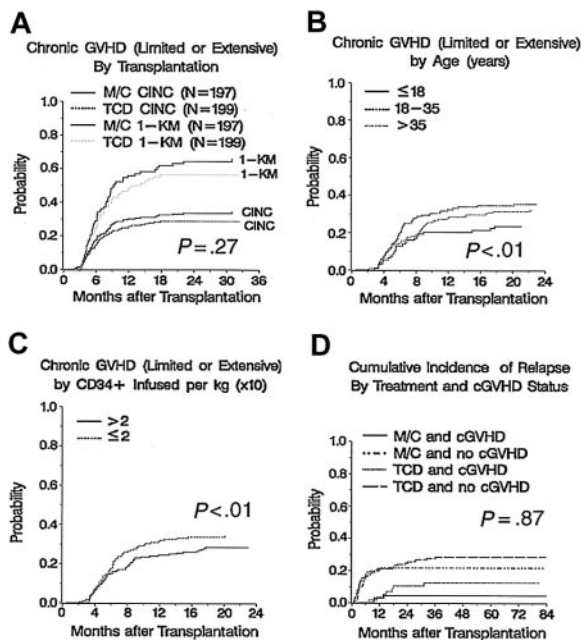


Figure 1. Cumulative incidence of chronic GVHD and relapse by covariates. (A) Cumulative incidence of chronic GVHD by treatment arm, $P = .27$. (B) Incidence of chronic GVHD by recipient age, $P < .01$. (C) Incidence of chronic GVHD by $CD34^+$ dose, $P < .01$. (D) Cumulative incidence of relapse by treatment arm and chronic GVHD status, $P = .87$.

Analysis of factors associated with risk of developing cGVHD is shown in Table 1. Although, in univariate analysis, primary disease other than CML was significant, in a multivariate Cox proportional hazards model, significant and independently favorable risk factors for decreased risk of cGVHD are younger recipient age ($P < .01$; Figure 1B), higher infused $CD34^+$ dose ($P \leq .01$; Figure 1C), and prior aGVHD of grade of 0 or I ($P \leq .01$).

Relapse

For all patients at 3 years, the relapse rate was 24% (95% CI, 18%-29%) for TCD patients and 16% (95% CI, 11%-20%) for M/C patients

($P = .08$). Patients who developed cGVHD had a significantly lower probability of relapse within both the TCD (28% versus 12%, $P < .01$) and M/C (22% versus 4%, $P < .01$) treatment arms (Figure 1D).

Characteristics of patients with chronic GVHD

Of 124 patients who developed cGVHD (TCD = 57, M/C = 67), 60% had diagnoses supported by histologic evidence. At the time of cGVHD diagnosis, 58% of the patients had more than one organ involved; 80% had a serum bilirubin less than 2.0 mg/dL. In 42% of cGVHD patients, platelet counts were less than 100 000/ μ L. Recipients with cGVHD in the TCD arm had less frequent prior acute GVHD (TCD 54% versus M/C 87%; $P < .01$) and a trend toward poorer performance status ($< 80\%$ Karnofsky score; TCD 50% versus M/C 32%; $P = .05$).

As shown in Figure 2, among those patients with cGVHD, more TCD patients had cutaneous involvement (TCD 68% versus M/C 50%; $P = .05$) and weight loss (TCD 21% versus M/C 6%; $P = .01$), but less often oral involvement (TCD 25% versus M/C 45%; $P = .02$). Rates of gastrointestinal or hepatic involvement, xerophthalmia, or obstructive lung disease were similar in both treatment arms.

Treatment of chronic GVHD

Most patients with cGVHD received prolonged systemic treatment with cyclosporine (95%), corticosteroids (87%), mycophenolate (26%), tacrolimus (21%), or azathioprine (13%). At 3 years from transplantation in patients with cGVHD, the CINC of being off all systemic immunosuppressive therapy was 63% (95% CI, 51%-75%) for TCD and 45% (95% CI, 34%-57%) for M/C ($P < .01$), but by 5 years the discontinuation rates were similar (TCD 72% versus M/C 63%; $P = .27$; Figure 3A).

Effect of chronic GVHD on incidence of serious infections

Among patients surviving at 100 days after transplantation, 81% of patients with cGVHD had a serious (severe, life-threatening, or fatal) infection as compared with 50% of patients who did not develop cGVHD ($P < .01$), irrespective of treatment arm. In patients diagnosed with cGVHD, treatment arm did not alter the

Table 1. Prognostic factors for developing cGVHD

Development of cGVHD	All patients, N = 404				
	CINC of cGVHD at 2 years	95% CI	Hazard ratio*	P	Favorable factors
Treatment arm					
M/C	0.34	0.27-0.40	1.22	.27	NA
TCD	0.29	0.22-0.35	1.00	NA	NA
Acute GVHD grade†					
					No prior aGVHD (0-1)
II-IV	NA	NA	1.84	< .01	NA
0-I	NA	NA	1.00	NA	NA
Recipient age					
					Younger recipients
Less than 19 years	0.23	0.14-0.32	1.00	NA	NA
18-35 years	0.35	0.27-0.43	2.51	< .01	NA
Greater than 35 years	0.32	0.25-0.40	2.44	< .01	NA
Primary disease					
					Diseases other than CML
CML	0.40	0.33-0.48	1.75	< .01	NA
Other	0.23	0.18-0.29	1.00	NA	NA
CD34+, infused/kg ($\times 10^6$)					
					Higher CD34+ infused
Less than or equal to 2.0	0.34	0.27-0.41	1.73	< .01	NA
Greater than 2.0	0.28	0.22-0.35	1.00	NA	NA

Variables that were considered and found not significant were date of transplantation, center, Karnofsky-Lansky performance status, sex of recipient and donor, donor age, HLA match, risk status, recipient and donor CMV status, recipient and donor race, method of T-cell depletion, T cells infused/kg, and total nucleated cell dose infused/kg.

NA indicates not applicable.

*Cox proportional hazards univariate analysis.

†Point estimates for aGVHD are not presented since it is a time-varying covariate.

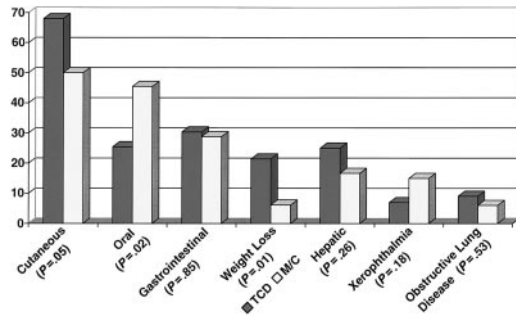


Figure 2. Chronic GVHD clinical manifestations at time of diagnosis.

frequency of serious infections ($P = .47$) or of bacterial ($P = .77$) or viral ($P = .57$) infections. However, among patients with cGVHD, those in the TCD arm had more fungal infections than those in the M/C arm ($P = .05$; Figure 4).

Survival and cause of death in patients with cGVHD

As shown in Figure 3B, the 3-year estimates of overall survival from transplantation for patients who developed cGVHD showed no significant difference between treatments: TCD 56% (95% CI, 43%-69%) and M/C 65% (95% CI, 54%-77%), $P = .30$.

Prognostic factors for survival from cGVHD onset are shown in Table 2. Although platelet count, primary disease risk status, and recipient CMV serology status, but not treatment arm, were suggestively important in univariate analysis, multivariate regression demonstrated that none of these factors had an independently significant impact on survival after the development of cGVHD. Multivariate analysis (Table 3; stratified on treatment arm) demonstrated that higher ($\geq 80\%$) Karnofsky-Lansky performance status ($P = .01$), prior aGVHD grade 0-I ($P = .03$), and HLA 6 of 6 match ($P = .03$) each favorably influenced overall survival in patients with cGVHD. The prognostic factors were the same in both arms.

Overall, 59 of the 124 patients with cGVHD died. Chronic GVHD was the most frequent primary cause of death resulting in 51 (86%) deaths (TCD, 25 and M/C, 26; Table 4). Infections were the major secondary cause of death. Only 6 patients died from relapse.

Discussion

Chronic GVHD remains a major obstacle for the long-term success of allogeneic HSCT.¹ Multiple studies have demonstrated the negative impact of cGVHD on survival and on quality of life and functional status in patients who survive and are cured of their hematologic malignancy. The primary objective of the present study was to deter-

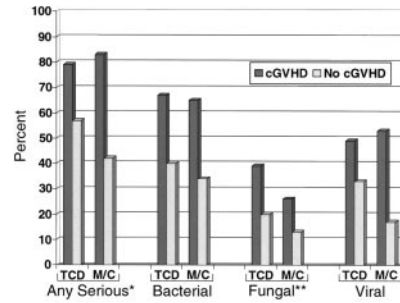


Figure 4. Serious infections in patients surviving 100 days after transplantation. All serious infections were more frequent in patients with cGVHD, * $P < .01$. Fungal infections were more frequent in patients with cGVHD after TCD, ** $P = .05$.

mine the effects of marrow TCD on the incidence, clinical manifestations, and consequences of cGVHD in a prospectively followed cohort of URD transplant recipients. Extensive and limited stages of cGVHD were combined, since these staging definitions have been poorly reproducible between transplantation centers.⁸

This analysis found that the incidence and time to development of cGVHD was similar in transplant patients receiving either TCD or M/C for GVHD prophylaxis after URD marrow transplantation. This differs from some earlier retrospective analyses in which URD TCD was usually associated with lesser risks of both acute and chronic GVHD.^{6,28} Of importance, in a randomized trial methotrexate was shown to not impact cGVHD incidence.²⁹ The mean T-cell depletion in this study was 1_{log} , which may be insufficient to protect against the development of cGVHD. However, ineffective prophylaxis of cGVHD using TCD despite lower risks of aGVHD may reflect differing pathogeneses of these 2 GVHD syndromes.^{30,31} The results of this prospective randomized trial are consistent with an earlier retrospective registry analysis in 870 mismatched related and URD HSCTs, which demonstrated consistently effective aGVHD prevention by a variety of ex vivo TCD methods, but no protection against cGVHD.¹⁶ In that study, the disparate effect of TCD in preventing acute but not chronic GVHD was particularly evident using TCD with narrow specificity anti-T-cell antibodies. These narrow spectrum techniques yielded an increased risk of cGVHD. This suggests that infusion of non-T-accessory cell populations may play a role in promoting cGVHD.¹⁶ In the current trial, two different TCD methodologies were used and conditioning regimens varied by the type of GVHD prophylaxis in order to promote engraftment; however, the study was designed to evaluate the whole treatment package and not its specific components.

Significant factors associated with cGVHD include older patient age and prior aGVHD. These have been identified in earlier reports.² The association of a higher CD34⁺ marrow cell dose with lower incidence of cGVHD is a new observation in URD transplantation and needs to be confirmed in future studies. One study of 50 patients after HLA-identical sibling bone marrow transplantation found a negative correlation between a higher number of marrow CD34⁺ cells ($> 3.12 \times 10^6/kg$) and probability of cGVHD.³² Two large cohort studies reported no correlation between the CD34⁺ cell dose and cGVHD in recipients of HLA-identical sibling bone marrow.^{33,34} In contrast, very high CD34⁺ cell dose ($> 8 \times 10^6/kg$) is a recognized risk factor for higher incidence and severity of cGVHD after peripheral blood allogeneic stem cell (PBSC) transplantation.³⁵⁻³⁷ This may reflect different importance of CD34⁺ cells or accompanying cell populations in the pathogenesis of cGVHD after marrow versus PBSC transplantation. The current study also confirms the protective effect of cGVHD in prevention of relapse. An average 1_{log} TCD of the bone marrow does not abrogate this cGVHD-associated antineoplastic effect.

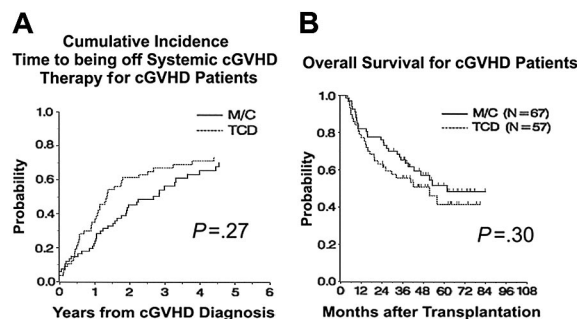


Figure 3. Time to being off systemic immunosuppressive therapy and overall survival from transplantation for patients with chronic GVHD. (A) Time to being off systemic immunosuppressive therapy for chronic GVHD, $P = .27$ at 5 years. (B) Overall survival from time of transplantation for patients with chronic GVHD, $P = .30$.

Table 2. Prognostic factors for survival in patients with cGVHD: univariate analysis

Patients with chronic GVHD, N = 124	Kaplan-Meier survival probability at 3 years	95% CI	Hazard ratio	P	Favorable factors
Treatment arm					
M/C	0.58	0.45-0.70	0.78	.29	NA
TCD	0.51	0.38-0.64	1.00	NA	NA
Performance status at cGVHD diagnosis					
Less than 80	0.34	0.20-0.48	2.66	< .01	Performance status of 80-100
Greater than or equal to 80	0.68	0.57-0.80	1.00	NA	NA
Platelet count at cGVHD diagnosis					
Less than 100 000	0.41	0.28-0.55	2.41	< .01	Platelet count \geq 100 000/ μ L
Greater than or equal to 100 000	0.71	0.59-0.83	1.00	NA	NA
Prior acute GVHD					
Grades II-IV	0.45	0.32-0.58	1.84	.02	Acute GVHD grade 0 or I
0 or I	0.65	0.52-0.77	1.00	NA	NA
HLA match					
6 of 6	0.58	0.48-0.69	0.59	.06	6 of 6 HLA match
5 of 6	0.42	0.23-0.60	1.00	NA	NA
Risk status					
Poor	0.38	0.17-0.58	2.04	.02	Good risk status
Good	0.58	0.48-0.68	1.00	NA	NA
Recipient CMV serostatus					
Negative	0.63	0.52-0.75	0.60	.05	Seronegative
Positive	0.42	0.28-0.57	1.00	NA	NA

NA indicates not applicable.

About 60% of patients with cGVHD had more than one organ involved, most commonly skin and/or oral mucosa. Chronic GVHD after TCD transplantation was associated with more frequent skin involvement and weight loss, but less oral involvement. Other regimen-related factors may confound interpretation of these differences. For example, a higher incidence of oral mucositis observed in the M/C cohort might predispose patients to a higher incidence of oral cGVHD.¹⁹

Time to discontinuation of systemic immunosuppression is a marker for success of therapy for cGVHD.^{38,39} At 5 years there was no difference in the proportion of patients completing immunosuppression, reflecting similar rates of cGVHD resolution in the 2 treatment arms.

Serious infections were more frequent in patients with cGVHD and were a major contributing cause of morbidity and mortality. More frequent fungal infections occurred in TCD patients with cGVHD, but the net adverse effect of cGVHD and its therapy were largely independent of the initial randomized treatment. The exact mechanism of immune compromise due to cGVHD or therapeutic treatment requires further research and new techniques to limit immune compromise.

Overall survival after diagnosis of cGVHD was similar in the TCD and M/C groups. Lower performance status, HLA mismatch, and preceding aGVHD were each independently associated with poorer survival in patients with cGVHD. Karnofsky score and aGVHD grade have been recognized as adverse prognostic factors in prior retrospective cohort studies.² A recent analysis emphasized

the increased risks of HLA-mismatch on nonrelapse mortality in patients with cGVHD after URD transplantation.³⁹

In summary, in this prospective randomized trial, despite reduction of aGVHD, an average I_{log} ex vivo TCD failed to reduce the incidence of cGVHD. The TCD methodologies used in this study were less intense than many TCD methodologies currently used, and these results may not necessarily be extrapolated to other TCD techniques. In patients developing cGVHD, overall survival was not impacted by treatment arm. Chronic GVHD was associated with more frequent serious infections, but also with effective protection against relapse in both the TCD and M/C cohorts. Nonrelapse mortality remains excessively high after cGVHD diagnosis, and developing better cGVHD prevention and treatment strategies represents a major task. Improved understanding of cGVHD biology and more refined graft manipulations are needed to increase the long-term success of URD marrow transplantation.

Acknowledgments

The authors are indebted to the work of many clinical investigators who have advanced the field and the many physicians and nurses who have diligently cared for these complex patients. In addition, we gratefully acknowledge the work of the many search coordinators and the dedicated staff of the National Marrow Donor Program.

Table 3. Final multivariate analysis: survival from cGVHD diagnosis

Survival	Hazard ratio	95% CI	P	Favorable factors
Performance status at diagnosis				
Less than 80	2.67	1.54-4.60	< .01	Performance status of 80-100
Greater than or equal to 80	1.00	NA	NA	NA
Acute GVHD grade				
II, III, or IV	1.99	1.09-3.63	.03	Acute GVHD grade 0 or I
0 or I	1.00	NA	NA	NA
HLA match				
5 of 6	1.92	1.05-3.57	.03	6 of 6 HLA match
6 of 6	1.00	NA	NA	NA

Stratified on treatment because of nonproportional hazards.
NA indicates not applicable.

Table 4. Causes of death for patients with cGVHD

Primary and secondary causes of death	TCD arm, n (%)	M/C arm, n (%)
Chronic GVHD	14 (48)	13 (43)
Chronic GVHD with infection*	11 (38)	13 (43)
Malignancy relapse	4 (14)	2 (7)
Other†	0 (0)	2 (3)
Total	29 (100)	30 (100)

*Chronic GVHD with a fatal infection.

†Breast cancer (n = 1), myocardial infarction (n = 1).

Appendix

Participating institutions and coinvestigators were University of Minnesota (Elutriation Center, n = 103; John E. Wagner, Jo-Anne van Burik, Stella M.

Davies, Shawn Fuller), Memorial Sloan-Kettering Cancer Center (T10B9 Center, n = 70; Richard O'Reilly, Nancy Collins), Medical College of Virginia (T10B9 Center, n = 53), Wake Forest University Baptist Medical Center (T10B9 Center, n = 36; David Hurd), University of Nebraska (Elutriation Center, n = 34; Thomas Gross, Michael Bishop), University of Utah (T10B9 Center, n = 33; Finn Petersen, Patrick Beatty), Stanford University (T10B9 Center, n = 25; Robert Negrin), University of Iowa (T10B9 Center, n = 19), University of South Carolina (T10B9 Center, n = 13; Adrian Gee), Ohio State University (T10B9 Center, n = 6; Edward Copelan), Duke University (T10B9 Center, n = 6; Joanne Kurtzberg), University of Kentucky (T10B9 Center, n = 5; John S. Thompson, Gordon Phillips), Medical College of Wisconsin (T10B9 Center, n = 4; Carolyn Keever-Taylor, William Drobycki, Neal Flomenberg), Western Pennsylvania Hospital (T10B9 Center, n = 2; Richard Shaddock), and University of Pittsburgh (T10B9 Center, n = 1; Albert Donnemberg); Craig Howe, Steering Committee Chairperson; Paul J. Martin, Fred Hutchinson Cancer Research Center; The EMMES Corporation (Donald Stablein, Elizabeth Wagner); and NHLBI (LeeAnn Jensen, Nancy Geller, Paul McCurdy).

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Prognostic Factors of Chronic Graft-Versus-Host Disease After Allogeneic Blood Stem-Cell Transplantation

Steven Z. Pavletic,^{1,3*} Lynette M. Smith,² Michael R. Bishop,³ James C. Lynch,²
Stefano R. Tarantolo,¹ Julie M. Vose,¹ Philip J. Bierman,¹ Abdul Hadi,¹
James O. Armitage,¹ and Anne Kessinger¹

¹Department of Internal Medicine, Section of Oncology–Hematology, University of Nebraska Medical Center, Omaha, Nebraska

²Department of Preventive and Societal Medicine, University of Nebraska Medical Center, Omaha, Nebraska

³National Cancer Institute, Bethesda, Maryland

Allogeneic hematopoietic stem cells in peripheral blood transplantation (alloPBSCT) or bone marrow transplantation (alloBMT) have different biological characteristics which may affect differently prognostic factors for incidence and severity of chronic graft-versus-host disease (cGVHD). To determine the prognostic factors of cGVHD in patients receiving alloPBSCT, data on 87 patients who survived at least 100 days after matched related donor myeloablative transplantation were analyzed. Factors significantly associated with higher incidence of cGVHD after alloPBSCT included CMV-positive donor, acute skin GVHD, and diagnoses other than lymphoma. Factors predictive for poor survival following cGVHD diagnosis included platelet count < 100,000/mm³ and history of acute liver GVHD. Acute liver GVHD and etoposide in the preparative regimen significantly increased risk of death due to cGVHD after alloPBSCT. All alloPBSCT multivariate models were fit to an independent cohort of comparable matched related donor alloBMT patients (*n* = 75). After alloBMT, only acute skin GVHD and diagnoses other than lymphoma retained prognostic significance for predicting cGVHD. Low platelet count was the only variable predictive for poor survival in cGVHD patients after alloBMT. Acute liver GVHD was the only factor that retained prognostic significance for risk of death due to cGVHD after alloBMT. These data suggest there are some cGVHD prognostic factors that may be unique to recipients of alloPBSCT. More studies are needed to determine whether cGVHD prognostic systems should be used interchangeably in patient populations receiving different stem-cell products. *Am. J. Hematol.* 78:265–274, 2005. © 2005 Wiley-Liss, Inc.

Key words: graft-versus-host; chronic; stem-cell transplantation; allogeneic

INTRODUCTION

Chronic graft-versus-host disease (cGVHD) is a systemic alloimmune and autoimmune disorder that can occur after allogeneic hematopoietic stem cell transplantation (alloHSCT) [1]. Chronic GVHD is characterized by immune dysregulation and immunodeficiency, resulting in impairment of multiple organ functions and decreased survival. A beneficial effect of cGVHD is a malignancy-associated decreased risk of relapse that is attributed to an allogeneic graft-versus-tumor (GVT) effect [2–4]. However, patients who are at low-risk for relapse and have severe manifestations of cGVHD experience increased transplant-related mortality, negating any cGVHD-associated GVT benefit [3,4]. Better treatment and prevention strategies for

cGVHD are needed. There is a paucity of well-planned clinical trials in cGVHD, and one of the serious obstacles is the lack of accepted staging and response criteria [5,6]. The current clinical classification that separates cGVHD in to limited versus extensive stage [7] has been criticized as poorly reproducible with marginal

*Correspondence to: Steven Z. Pavletic, M.D., Head, Graft-Versus-Host and Autoimmunity Unit, Experimental Transplantation and Immunology Branch, National Cancer Institute, 9000 Rockville Pike, Building 10, Room CRC 3-3330, Bethesda, MD 20892-1907.
E-mail: pavletis@mail.nih.gov

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prognostic value [1,4]. Two new cGVHD prognostic systems have been proposed based on one large registry-based analysis and one single-institution analysis [4,8]. Both prognostic systems were formulated from clinical observations of patients who almost exclusively received allogeneic bone marrow transplant (alloBMT).

Growth-factor-mobilized allogeneic blood stem cells have been increasingly used as a source for transplantation rather than marrow [9–11]. Cellular composition, functional status, and cytokine expression profiles of alloPBSCT grafts are much different than those of alloBMT grafts [9–15]. The rate of immunological reconstitution after alloPBSCT is faster and qualitatively different than after alloBMT [9,16,17]. The incidence and severity of cGVHD after alloPBSCT are increased in most studies, and cGVHD may be more difficult to treat after alloPBSCT [18–20]. Differences in immunogenic and reconstitutive characteristics between these two stem-cell sources may explain different post-transplant outcomes, including the incidence of cGVHD [11,21]. Hypothetically, these differences may also modify prognostic factors for cGVHD. The assumption that prognostic factors identified in alloBMT patients could be equally applied in the alloPBSCT setting may be inaccurate. Currently, prognostic factors for cGVHD severity in patients transplanted with alloPBSCT are unstudied. We examined prognostic factors for cGVHD onset, survival, and mortality in a group of long-term survivors after alloPBSCT who received HLA-matched related donor grafts. To determine whether prognostic factors identified in alloPBSCT may be applicable after alloBMT, the prognostic factors were tested on an independent sample of alloBMT patients who received identical GVHD prophylaxis regimens.

PATIENTS AND METHODS

Selection of Patients

Adult patients with hematologic malignancy consented to participate in University of Nebraska Medical Center IRB-approved studies of high-dose therapy and alloHSCT from an HLA-matched related donor. Eighty-seven patients (84 sibling donors, 3 parent donors) who received alloPBSCT between December 1994 and November 1998 and 75 (74 sibling donors, 1 parent donor) patients who received alloBMT between January 1990 and September 1998 and survived at least 100 days post-transplant were included in this analysis. Exclusion criteria included prior high-dose HSCT, less than fully matched (HLA-A, B, and DRB1) donor, and identical twin donor. There was an additional 31 alloPBSCT patients (of total $n = 118$) and 23 alloBMT patients (of total $n = 98$) who fit the

eligibility criteria and were transplanted in the same time frame that died before 100 days. The information on cGVHD was retrieved from patients' records using pre-designed data forms.

Transplant Regimen

Peripheral blood stem cells were mobilized from normal donors with recombinant G-CSF (filgrastim), collected with leukapheresis, and cryopreserved [10]. Bone marrow was harvested using standard methods and immediately infused. Conditioning regimens included cyclophosphamide (120 mg/kg) and total-body irradiation (1,200 cGy), with or without etoposide (1,800 mg/m²). Etoposide was given based on the transplant protocol available at the time of patient enrollment, independently of the underlying disease status. If irradiation was contraindicated, patients received busulfan (16 mg/kg) instead. Two patients received cytarabine with total-body irradiation or fludarabine. GVHD prophylaxis consisted of cyclosporine (target serum level 200–300 ng/L) and methotrexate (5 mg/m² on days 1, 3, 6, and 11). Immunosuppressive drugs were tapered beginning 100 days post-transplant if no signs of GVHD were evident and were gradually discontinued over 3 months.

Chronic GVHD Diagnosis and Treatment

Patients were evaluated for GVHD weekly until day 100 post-transplant, every 3 months thereafter until 2 years post-transplant, and then yearly until 5 years post-transplant. The diagnosis and stage of cGVHD were determined using established clinical and pathologic criteria [7]. First-line treatment for cGVHD included cyclosporine and prednisone [22]. Salvage therapy medications for cGVHD were chosen according to institutional guidelines or research protocols available at the time of treatment.

Statistics

Primary endpoints of this analysis were (a) incidence of cGVHD (extensive or limited stage), (b) impact of cGVHD on overall survival, (c) overall survival following cGVHD, and (d) incidence of cGVHD-specific mortality (deaths in patients with cGVHD without post-transplant malignancy relapse). The variables included in the regression analysis of all day 100 survivors are shown in Table I. Additional variables were analyzed to determine prognostic factors at the time of cGVHD diagnosis (Table II). All variables were used as dichotomized values (yes/no). Patient clinical characteristics were compared between the alloPBSCT group and the alloBMT group using Fisher's exact test and the

TABLE I. Clinical Characteristics of Transplanted Patients

	AlloPBSCT (n = 87)	AlloBMT (n = 75)	P value
Median age in years at transplant (range)	40 (20–60)	37 (17–60)	0.0026
Female: n (%)	38 (44%)	37 (49%)	0.53
White, non-Hispanic: n (%)	83 (95%)	73 (97%)	0.69
Disease: n (%)			
Leukemia/MDS	54 (62%)	59 (79%)	0.067
Lymphoma	28 (32%)	14 (19%)	
Multiple Myeloma	5 (6%)	2 (3%)	
High relapse risk: n (%) ^a	46 (53%)	36 (48%)	0.64
CMV-negative recipient: n (%)	42 (48%)	44 (59%)	0.21
HSV-negative recipient: n (%)	18 (22%)	19 (29%)	0.35
Etoposide: n (%)	18 (21%)	69 (92%)	< 0.0001
TBI: n (%)	81 (93%)	67 (89%)	0.42
History of smoking: n (%)	53 (62%)	59 (80%)	0.023
Median age in years of donor (range)	42 (18–73)	37 (6–62)	0.0043
Female donor: n (%)	42 (48%)	32 (43%)	0.53
CMV-negative donor: n (%)	42 (49%)	34 (46%)	0.75
Days to 500 neutrophils (range)	12 (9–23)	18 (10–73)	< 0.001
Days to 500 lymphocytes (range)	19 (9–228)	41 (10–475)	< 0.001
Median CD34 dose/kg (10 ⁶) (range)	8.12 (1.77–37.9)	ND	—
Median CD3 dose/kg (10 ⁸) (range)	5.97 (1.73–12.76)	ND	—
Median MNC dose/kg (10 ⁸) (range)	9.08 (2.95–16.84)	ND	—
< 4 MTX number of doses (%)	14 (17%)	16 (38%)	0.014
Missing	5	33	
< 100 K Platelets at day 100 (%)	18 (23%)	10 (20%)	0.83
Missing	5	33	
Prior AGVHD grade: n (%)			
0	23 (26%)	24 (32%)	0.10
I	13 (15%)	17 (23%)	
II	33 (38%)	23 (31%)	
III	12 (14%)	11 (15%)	
IV	6 (7%)	0 (0%)	
AGVHD GI stage: n (%)			
0 = none	58 (67%)	52 (69%)	0.74
1–4 = mild/severe	29 (33%)	23 (31%)	
AGVHD liver stage: n (%)			
0 = none	71 (82%)	61 (82%)	1.00
1–4 = mild/severe	16 (18%)	13 (18%)	
AGVHD skin stage: n (%)			
0 = none	39 (45%)	28 (37%)	0.34
1–4 = mild/severe	48 (55%)	47 (63%)	
AGVHD upper GI stage: n (%)			
0 = none	23 (26%)	24 (32%)	0.49
1–4 = mild/severe	64 (74%)	51 (68%)	

^aPatients at low risk of malignancy relapse were those with acute leukemia in first remission, chronic myelogenous leukemia in first chronic phase, myelodysplastic syndromes without increased blasts, and lymphoma or chronic lymphocytic leukemia in remission or untreated first relapse. All multiple myeloma patients who underwent transplant were considered to be at high risk.

Wilcoxon rank sum tests. Log-rank tests were used to compare the distributions of time to event variables.

Univariate Cox regression analysis was used to estimate relative risks and 95% confidence intervals for risk factors of incidence of cGVHD, overall survival, overall survival following cGVHD, and cGVHD-specific mortality for alloPBSCT cases. Time of cGVHD onset was calculated as time from transplant to cGVHD. Overall survival was calculated as time from transplant to death from any cause or date of last

contact. Overall survival following cGVHD was calculated as time from date of diagnosis of cGVHD to death from any cause or date of last contact. Chronic GVHD-specific mortality time was calculated as time from transplant to date of cGVHD-specific death. Multivariate models were fit with Cox stepwise regression to the alloPBSCT data for all four primary outcomes. The significance level used for variables to be entered and removed from the models was 0.05. The set of significant predictors in the alloPBSCT setting were

TABLE II. Clinical Characteristics of Patients With Chronic Graft-Versus-Host Disease After Allogeneic Stem-Cell Transplantation

	AlloPBSCT (n = 66)	AlloBMT (n = 47)	P value
Months from transplant to cGVHD (range)	6.3 (3.2–35.7)	5.6 (2.9–75.4)	0.17
Type of cGVHD onset: n (%)			
Progressive	12 (18%)	11 (24%)	0.65
Quiescent	40 (61%)	24 (53%)	
De novo	14 (21%)	10 (22%)	
Missing	—	2	
Stage: n (%)			
Limited	18 (27%)	18 (38%)	0.23
Extensive	48 (73%)	29 (62%)	
Skin involvement: n (%)	55 (83%)	33 (70%)	0.11
Eye involvement: n (%)	37 (56%)	20 (43%)	0.18
Mouth involvement: n (%)	46 (70%)	25 (53%)	0.080
Lung involvement: n (%)	6 (9%)	5 (11%)	1.00
GI tract involvement: n (%)	20 (30%)	12 (26%)	0.67
Liver involvement: n (%)	20 (30%)	20 (43%)	0.23
GU tract involvement: n (%)	7 (11%)	3 (6%)	0.52
Musculoskeletal involvement: n (%)	5 (8%)	4 (9%)	1.00
Scleroderma: n (%)	23 (35%)	12 (29%)	0.53
Karnofsky score < 80% at cGVHD: n (%)	10 (16%)	12 (26%)	0.23
Bilirubin > 2 mg/dL at cGVHD: n (%)	9 (16%)	6 (14%)	1.00
Platelets < 100 K at cGVHD: n (%)	15 (27%)	18 (41%)	0.20
Biopsy proven: n (%)	39 (61%)	26 (55%)	0.57

then fit to Cox models of the alloBMT data. To investigate the impact of cGVHD on overall survival, cGVHD is treated as a time-dependent variable after adjusting for other significant predictors of overall survival. The Kaplan–Meier method was used to estimate the distributions of overall survival and survival following cGVHD, and the cumulative incidence estimator was used to estimate the rates of cGVHD and cGVHD-specific mortality. Statistical analyses were completed with SAS software, Version 8.1 (SAS Institute Inc., Cary, NC).

RESULTS

Patient Characteristics

Patient characteristics for alloPBSCT and alloBMT cohorts are presented in Table I. The median follow-up of those alive at the last contact was 3.0 years (range 1–6 years) in the alloPBSCT group and 6.0 years (range 2–10 years) in the alloBMT group. No statistical difference was found between alloPBSCT and alloBMT groups, 3-year rates of survival were 60% (95% CI: 49–70%) versus 61% (95% CI: 50–72%), $P = 0.70$; malignancy progression 15% (95% CI: 2–29%) versus 19% (95% CI: 6–31%), $P = 0.56$; and incidence of

cGVHD 76% (95% CI: 45–100%) versus 59% (95% CI: 35–82%), $P = 0.22$. Clinical characteristics of the 66 patients who developed cGVHD after alloPBSCT and the 47 after alloBMT are shown in Table II. There were no significant differences in cGVHD characteristics between the two cohorts.

Risk Factors for Chronic GVHD After AlloPBSCT

Cox regression modeling was applied to the 87 alloPBSCT recipients. Acute GVHD grade variables were grouped as 0 versus I–IV because such grouping gave the best separation of the cumulative incidence curves. Variables associated with cGVHD in univariate analysis were lymphocyte recovery time less than the median time of 19 days (RR = 1.8, 95% CI: 1.1–3.0, $P = 0.019$), CMV-positive donor (RR = 1.8, 95% CI: 1.1–2.9, $P = 0.024$), prior history of acute GVHD skin stage 1–4 (RR = 1.8, 95% CI: 1.1–2.9, $P = 0.026$), and patient age > 40 years (RR = 1.7, 95% CI: 1.0–2.7, $P = 0.040$). Diagnosis of lymphoma was associated with decreased risk of cGVHD (RR = 0.5, 95% CI: 0.3–0.9, $P = 0.0092$). Donor age was not a significant factor predicting cGVHD. In multivariate analysis, CMV-positive donor (to any recipient), prior acute skin GVHD, and diagnoses other than lymphoma were significant predictors of cGVHD (Fig. 1a–c).

Impact of cGVHD on Survival After AlloPBSCT

Independent predictors of decreased overall survival after alloPBSCT were high relapse risk (RR = 3.5, 95% CI: 1.6–7.5, $P = 0.0018$), history of smoking (RR = 2.3, 95% CI: 1.1–4.5, $P = 0.023$), and acute liver GVHD (RR = 2.2, 95% CI: 1.1–4.6, $P = 0.029$). A diagnosis of lymphoma was a good prognostic indicator (RR = 0.4, 95% CI: 0.2–0.9, $P = 0.032$). After adjusting for significant predictors of overall survival, we observed that the occurrence of cGVHD significantly predicted poor survival (RR = 2.8, 95% CI: 1.2–6.6, $P = 0.018$).

Survival After cGVHD Diagnosis in AlloPBSCT

To determine the factors that predict survival after cGVHD diagnosis, we analyzed survival after the occurrence of cGVHD in the 66 alloPBSCT patients with cGVHD. Predictors that were significant in the univariate analysis are presented (Table III). Extensive cGVHD did not predict poor survival after alloPBSCT (RR 1.9, $P = 0.21$). Skin and oral involvement were associated with better survival (Table III). In multivariate analysis, predictive factors for poor survival at 3 years following cGVHD diagnosis were platelets < 100,000/mm³ [0% (95% CI: undefined) vs. 79% (95% CI: 65–93%), $P < 0.001$] and history of acute

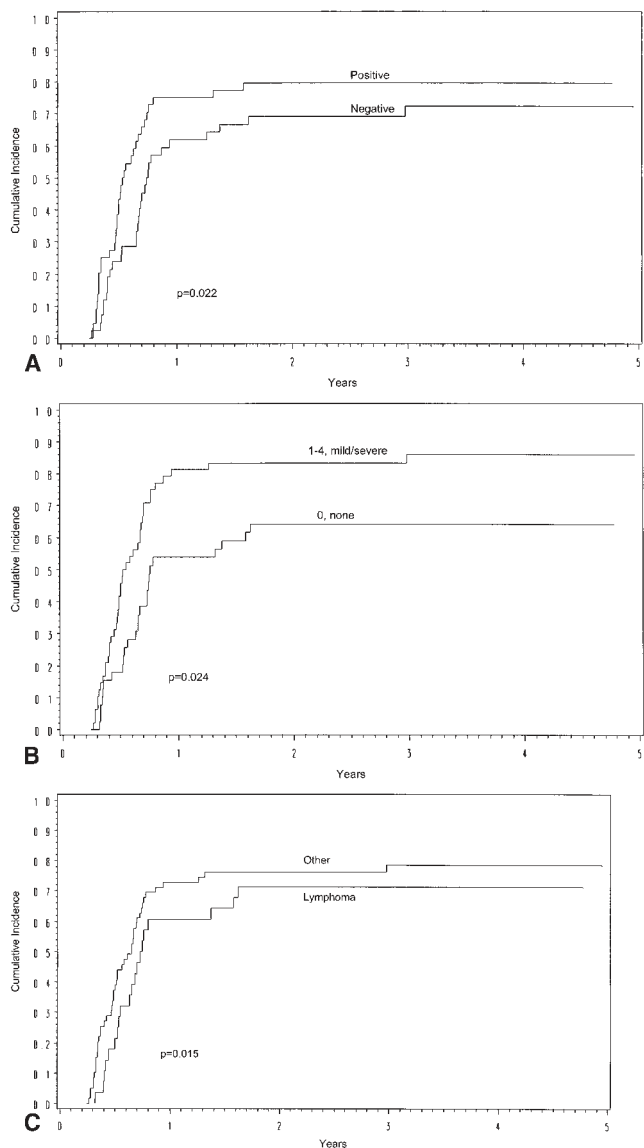


Fig. 1. Cumulative incidences of chronic GVHD after allogeneic blood stem-cell transplantation according to prognostic factors that were identified in the multivariate analysis. Only patients who survived at least 100 days post-transplant were included (n = 87). (A) Patients with donors who were cytomegalovirus (CMV) serology positive versus seronegative donors. (B) Patients who developed acute GVHD of the skin (stages 1–4) versus those who did not. (C) Patients with diagnosis of lymphoma versus others.

GVHD of the liver [42% (95% CI: 14–70%) vs. 59% (95% CI: 41–76%), *P* = 0.0088] (Fig. 2a,b).

Chronic GVHD-Specific Mortality After AlloPBSCT

To identify the individuals that are likely to succumb from cGVHD, 87 alloPBSCT 100-day survivors were analyzed for factors predicting cGVHD-specific mortality (death with cGVHD and no post-transplant progression of malignancy). Factors predictive for

TABLE III. Univariate Analysis: Risk Factors Predicting Overall Survival in Allogeneic Blood Stem Cell Transplantation Patients at Chronic Graft-Versus-Host Disease Diagnosis (n = 66)

Risk factor	RR (95% CI)	<i>P</i> value
Variables through first 100 days		
< 50,000/mm ³ platelets at day 100	3.3 (1.5–7.1)	0.0025
Acute GVHD liver	2.8 (1.3–6.4)	0.012
Variables at chronic GVHD diagnosis		
Platelets < 100,000/mm ³	12.5 (4.9–32.0)	< 0.0001
Progressive vs. de novo	7.9 (1.6–38.2)	0.010
Biopsy proven, liver	4.9 (1.7–14.3)	0.0037
Bilirubin > 2.0 mg/dL	4.2 (1.6–10.9)	0.0039
Karnofsky score < 80%	3.2 (1.4–7.4)	0.0075
< 6.3 months from transplant	2.8 (1.2–6.4)	0.015
GI tract involvement	2.5 (1.2–5.4)	0.018
Biopsy proven	2.4 (1.0–5.8)	0.049
Liver involvement	2.2 (1.0–4.7)	0.044
Mouth involvement	0.4 (0.2–0.8)	0.011
Skin involvement	0.3 (0.1–0.7)	0.0065

GVHD-specific mortality in the univariate analysis were acute liver GVHD (RR = 4.0, 95% CI: 1.7–9.8, *P* = 0.002), etoposide in the preparative regimen (RR = 3.0, 95% CI: 1.2–7.1, *P* = 0.016), < 4 total doses of methotrexate (RR = 2.9, 95% CI: 1.1–7.7, *P* = 0.028), and platelets < 50,000/mm³ on day 100 (RR = 2.5, 95% CI: 1.0–5.9, *P* = 0.041). Results of the stepwise selection of Cox regression were used as a multivariate model of cGVHD-specific mortality. Prior acute GVHD of the liver and etoposide in the preparative regimen significantly predicted death from cGVHD (Fig. 3a,b), and 3-year cumulative incidences of cGVHD-specific mortality were 38% (95% CI: 0–85%) for acute liver GVHD versus 18% with no prior aGVHD of the liver (95% CI: 2–34%) and 39% (95% CI: 5–73%) in recipients of etoposide versus 17% with no etoposide (95% CI: 0–34%).

Validation of AlloPBSCT Risk Factors in AlloBMT Recipients

To assess the validity of alloPBSCT prognostic factors in alloBMT recipients, all alloPBSCT multivariate variables were fit to the patient data obtained from the independent cohort of alloBMT patients. Only acute GVHD of the skin and diagnosis other than lymphoma retained their prognostic significance for the onset of cGVHD after alloBMT (Table IV, section a). Development of cGVHD was not significantly predictive of poor overall survival after alloBMT (RR = 1.9, 95% CI: 0.9–4.1, *P* = 0.11). When prognostic factors for survival after diagnosis of cGVHD were applied to the alloBMT group, only low platelet count remained predictive for poor survival (Table IV, section b). Of interest, prior acute GVHD of the liver had no predictive value for survival in cGVHD patients after

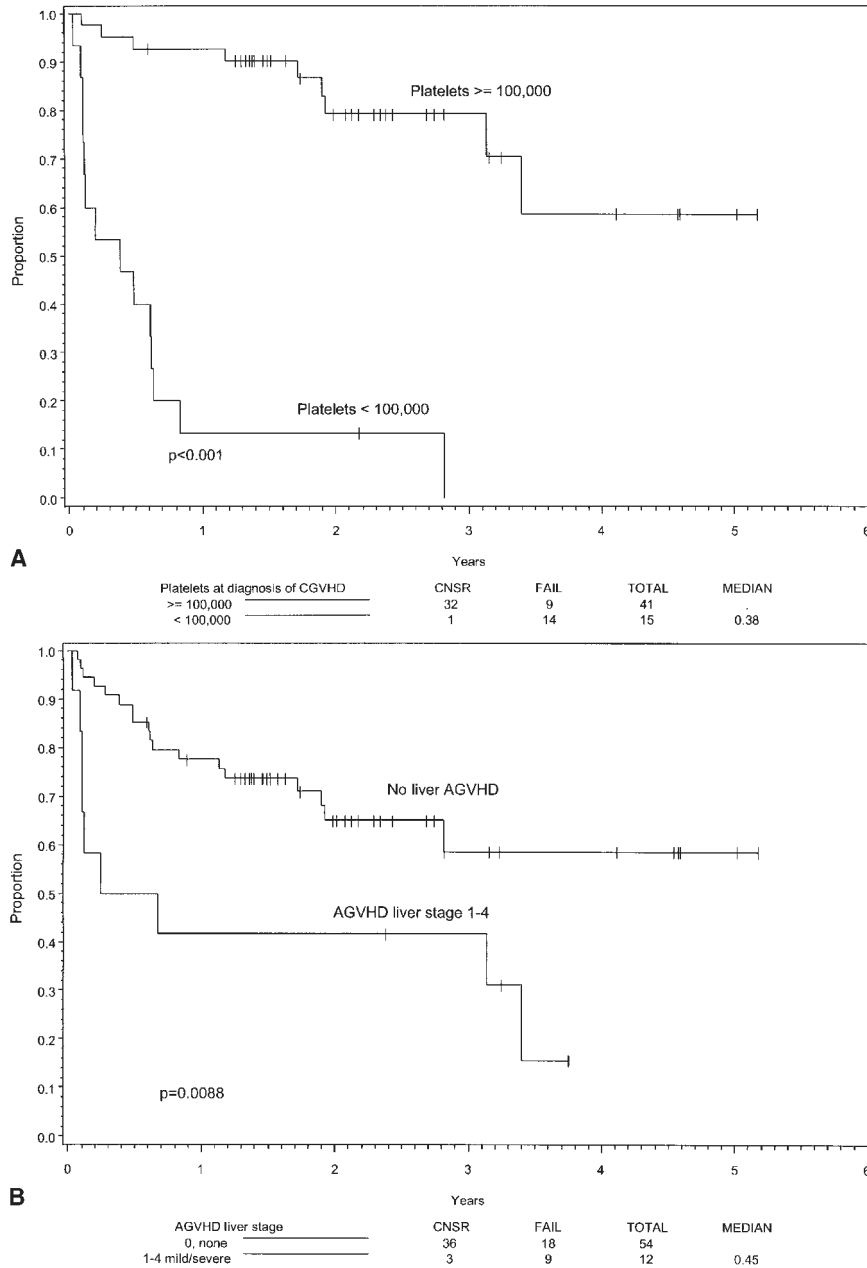


Fig. 2. Survival following chronic GVHD after allogeneic blood stem-cell transplantation according to prognostic factors identified in the multivariate analysis. Only patients who developed cGVHD are included ($n = 66$). (A) Patients with more versus less than $100,000/\text{mm}^3$ platelets at cGVHD diagnosis. (B) Patients without prior history of acute GVHD of the liver versus those with prior acute liver GVHD.

alloBMT. Prior history of acute liver GVHD (but not of prior etoposide) remained significantly predictive for the cGVHD-specific mortality in the alloBMT cohort (Table IV, section c).

DISCUSSION

The goal of this study was to define prognostic factors of cGVHD incidence and severity in a patient

population that received exclusively alloPBSCT stem cells. We also addressed if these factors would be applicable in patients who received alloBMT. The incidence of cGVHD in the current alloPBSCT series was 76%, which is within the range of 44% to 100% observed in other clinical trials [23]. The majority of patients in this study had a quiescent type of cGVHD onset (61%); the most commonly involved organs were skin, eyes, and mouth. Because classification of

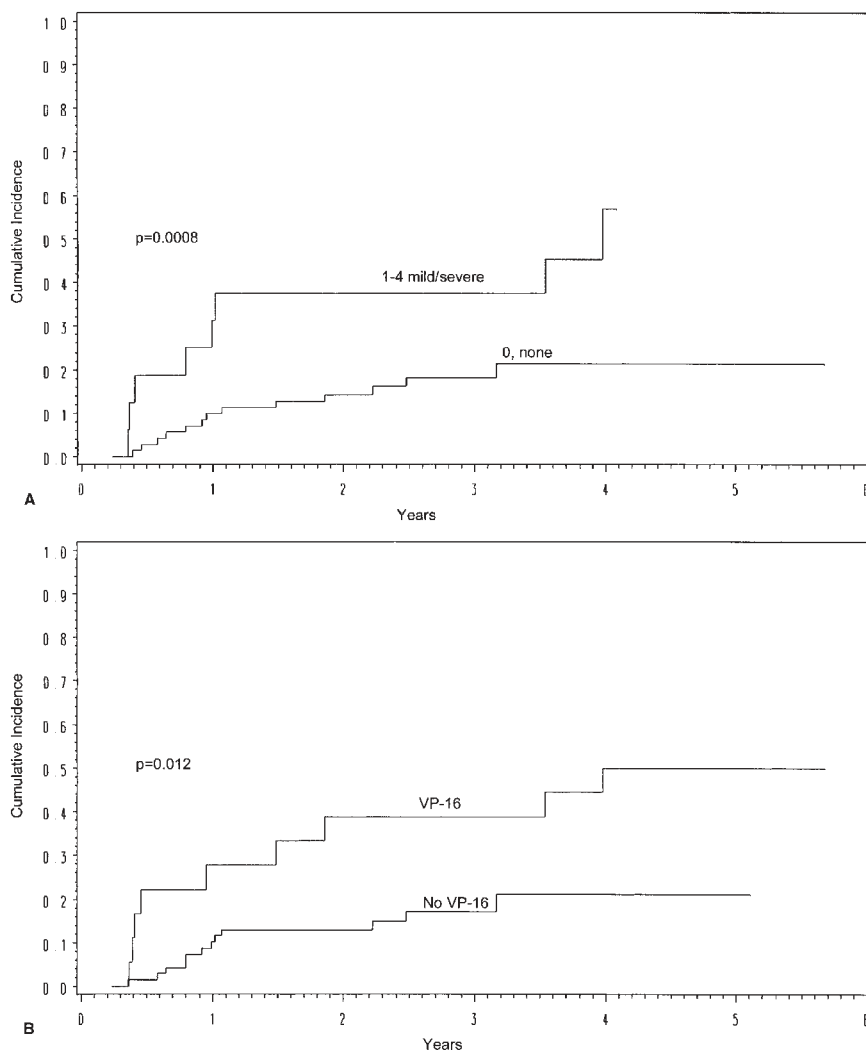


Fig. 3. Cumulative incidences of chronic GVHD-specific mortality after allogeneic blood stem-cell transplantation according to prognostic factors that were identified in the multivariate analysis. Only patients who survived at least 100 days post-transplant were included ($n = 87$). (A) Patients with prior history of acute GVHD of the liver versus those without prior liver GVHD. (B) Patients who received etoposide in the preparative regimen versus those who did not receive prior etoposide.

extensive and limited-stage cGVHD has been widely criticized and our own analyses showed that extensive stage was not predictive for cGVHD-specific survival, overall incidence of cGVHD (extensive or limited) was selected as the major endpoint of this study.

In alloPBSCT patients, CMV-positive donor serology was significantly associated with a high incidence of cGVHD. Other studies of alloPBSCT donors found no association of CMV status and cGVHD [24,25]. CMV infections induce anti-CD13 autoantibodies that are associated with the development of cGVHD skin manifestations [26]. In addition to the prognostic impact of the overall acute GVHD grade, we also analyzed the correlation of acute GVHD organ stage with the risk of cGVHD. The only acute GVHD organ manifestation

that correlated with cGVHD development was the skin. This correlation was found in both the alloPBSCT and the alloBMT groups. Because the skin was most commonly involved with acute GVHD, this correlation supports the theory of a common pathophysiological pathway in both acute and chronic GVHD [27]. A diagnosis of lymphoma was significantly associated with decreased risk of cGVHD in both alloPBSCT and alloBMT patients, a factor not commonly analyzed in other studies [1,24,25,28]. One possible explanation may be that different types of prior therapies used in patients with myeloid leukemia versus lymphoma affect the cytokine environment and resultant accessory cell function, which can modify allogeneic graft-versus-host reactions [29,30]. No prognostic impact of the

TABLE IV. Chronic Graft-Versus-Host Disease Prognostic Factors After Allogeneic Blood Stem-Cell Transplantation Identified in the Multivariate Analysis and Applied to the Independent Cohort of Allogeneic Bone Marrow Transplantation Patients*

(a) Factors predicting cGVHD after transplantation				
Risk factor	AlloPBSCT (<i>n</i> = 87)		AlloBMT (<i>n</i> = 75)	
	RR (95% CI)	<i>P</i> value	RR (95% CI)	<i>P</i> value
CMV+ donor ^a	2.5 (1.4–4.4)	0.0017	1.1 (0.5–2.6)	0.82
Acute GVHD, skin	2.0 (1.1–3.7)	0.018	4.8 (1.7–13.2)	0.0026
Lymphoma	0.5 (0.3–0.9)	0.022	0.1 (0.0–0.8)	0.028
(b) Factors predicting overall survival after cGVHD diagnosis				
Risk factor	AlloPBSCT (<i>n</i> = 66)		AlloBMT (<i>n</i> = 47)	
	RR (95% CI)	<i>P</i> value	RR (95% CI)	<i>P</i> value
Platelets < 100 K	25.9 (5.7–118.4)	<0.0001	3.0 (1.3–7.0)	0.010
Acute GVHD, liver ^a	12.0 (2.8–52.0)	0.0009	1.7 (0.6–4.5)	0.29
(c) Factors predicting cGVHD-specific mortality after transplantation				
Risk factor	AlloPBSCT (<i>n</i> = 87)		AlloBMT (<i>n</i> = 75)	
	RR (95% CI)	<i>P</i> value	RR (95% CI)	<i>P</i> value
Acute GVHD, liver	3.3 (1.2–8.9)	0.017	2.9 (1.0–8.3)	0.044
Etoposide ^a	2.9 (1.1–7.3)	0.029	1.4 (0.2–10.5)	0.76

*Abbreviations: MTX, methotrexate; CMV, cytomegalovirus; RR, relative risk.

^aprognostic factors significant after alloPBSCT but not after alloBMT.

CD34⁺ cell dose on the incidence of cGVHD was identified in the alloPBSCT patients. Others have found that CD34⁺ cell doses > 8 × 10⁶/kg recipient weight are associated with higher risks of cGVHD in a T-cell-replete alloPBSCT setting [21]. An explanation for this possible role of CD34⁺ cell dose is unknown. Perhaps CD34⁺ cells are a marker for other graft-related characteristics implicated in cGVHD pathogenesis rather than being directly associated with cGVHD pathogenesis [31]. The lack of prognostic value of CD34⁺ cell numbers in the current study may be due to differences in patient populations, transplantation protocols, or study design.

One of the most concerning effects of cGVHD is its adverse impact on survival. A chronic GVHD diagnosis significantly and independently predicted poor overall survival after alloPBSCT in this study. Independent factors that were strongly predictive for poor survival after cGVHD diagnosis were low platelets and a history of a clinical diagnosis of acute liver GVHD. A low platelet count in cGVHD patients is one of most consistent and most powerful poor-survival indicators across all cGVHD studies in both alloBMT and alloPBSCT settings. The identification of prior clinical diagnosis of acute GVHD of the liver as a poor prognostic factor for survival in alloPBSCT patients with cGVHD is a new observation; however, the impact of specific organ involvement by acute GVHD on survival in cGVHD was not addressed in prior studies, which

makes comparisons with literature data difficult [1,20,24,25,28]. History of clinical acute liver GVHD after alloBMT was not a significant predictor for survival, and the reason for this difference from alloPBSCT remains unclear. By the nature of the acute GVHD clinical grading system, diagnosis of liver acute GVHD is typically based on elevated bilirubin in the context of a biopsy-proven acute GVHD of another organ that is more accessible to biopsy, therefore other confounding clinical factors could affect such survival analyses.

In contrast to the report by Akpek et al. in alloBMT patients [8], skin involvement by cGVHD was associated with better survival in this alloPBSCT series (RR = 0.3, *P* = 0.0065). We could not identify an explanation for this positive role of skin involvement in survival as there were no significant associations with other prognostic factors (data not shown). Theoretically, there could be differences in survival between different types of cGVHD skin manifestations, such as lichenoid (an earlier manifestation) and sclerodermatous (a later manifestation). Such detailed information is not routinely collected in cGVHD studies, and it would be of interest to collect such data in future prospective studies of cGVHD. Oral involvement was another favorable factor for survival (RR = 0.4, *P* = 0.011), confirming observations by others [4,32]. Other commonly known predictive factors for survival after cGVHD diagnosis from marrow transplantation

studies such as progressive type of onset, low Karnofsky performance status, elevated bilirubin, and gastrointestinal involvement all were identified here as significant in the univariate but not the multivariate analysis; however, such a lack of significance may be also due to the limited sample size.

Identifying patients at elevated risk of mortality from cGVHD was an objective of this study. Our goal was to define the population at day 100 post-transplant that may need to be targeted in future trials searching for effective cGVHD surveillance and prevention strategies. Prior clinical diagnosis of acute liver GVHD was the most predictive for cGVHD-related deaths in both the alloPBSCT and alloBMT groups. Prior etoposide in the preparative regimen was prognostic for poor survival in the alloPBSCT cohort of cGVHD patients. We could not reliably identify whether administration of etoposide in conjunction with cyclophosphamide and total body irradiation was a poor predictor of survival in cGVHD patients in the alloBMT cohort due to a very high proportion of alloBMT patients receiving etoposide in the conditioning regimen. Theoretically, use of fresh marrow-derived stem cells versus cells cryopreserved from the blood product could affect post-transplant outcomes including GVHD; however, comparative studies did not substantiate such concerns [33]. Differences in cGVHD prognostic factors between alloBSCT and alloBMT may also be a consequence of confounding patient characteristics, too low a patient number in each group, or the retrospective nature of the study. Nevertheless, all patients were treated in the same institution and received the same GVHD prophylaxis and standardized supportive care.

In summary, we identified several independent prognostic factors of cGVHD incidence and severity in a group of patients that all received alloPBSCT stem cells. Some of prognostic factors identified in alloPBSCT patients may not be applicable to the alloBMT recipients. More studies are needed to determine whether cGVHD prognostic systems may be used interchangeably in patient populations receiving different stem-cell products.

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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

Steven Z. Pavletic,¹ Paul Martin,² Stephanie J. Lee,³ Sandra Mitchell,¹ David Jacobsen,⁴ Edward W. Cowen,¹ Maria L. Turner,¹ Gorgun Akpek,⁵ Andrew Gilman,⁶ George McDonald,² Mark Schubert,² Ann Berger,⁷ Peter Bross,⁸ Jason W. Chien,² Daniel Couriel,⁹ J. P. Dunn,¹⁰ Jane Fall-Dickson,¹¹ Ann Farrell,⁸ Mary E. D. Flowers,² Hildegard Greinix,¹² Steven Hirschfeld,⁸ Lynn Gerber,⁷ Stella Kim,⁹ Robert Knobler,¹² Peter A. Lachenbruch,⁸ Frederick W. Miller,¹³ Barbara Mittleman,¹⁴ Esperanza Papadopoulos,¹⁵ Susan K. Parsons,¹⁶ Donna Przepiorka,¹⁷ Michael Robinson,¹⁸ Michael Ward,¹⁴ Bryce Reeve,¹ Lisa G. Rider,¹³ Howard Shulman,² Kirk R. Schultz,¹⁹ Daniel Weisdorf,²⁰ Georgia B. Vogelsang¹⁰

¹National Cancer Institute, National Institutes of Health, Bethesda, Maryland; ²Fred Hutchinson Cancer Research Center, University of Washington School of Medicine, Seattle, Washington; ³Dana-Farber Cancer Institute, Boston, Massachusetts; ⁴Children's Memorial Hospital, Northwestern University School of Medicine, Chicago, Illinois; ⁵University of Maryland School of Medicine, Baltimore, Maryland; ⁶University of North Carolina School of Medicine, Chapel Hill, North Carolina; ⁷Warren Grant Magnuson Clinical Center, National Institutes of Health, Bethesda, Maryland; ⁸US Food and Drug Administration, Rockville, Maryland; ⁹University of Texas M.D. Anderson Cancer Center, Houston, Texas; ¹⁰Johns Hopkins University School of Medicine, Baltimore, Maryland; ¹¹National Institute of Nursing Research, National Institutes of Health, Bethesda, Maryland; ¹²Medical University of Vienna, Austria; ¹³National Institute of Environmental Health Sciences, National Institutes of Health, Bethesda, Maryland; ¹⁴National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, Maryland; ¹⁵Memorial Sloan-Kettering Cancer Center, New York, New York; ¹⁶Tufts-New England Medical Center, Boston, Massachusetts; ¹⁷University of Tennessee, Memphis, Tennessee; ¹⁸National Eye Institute; National Institutes of Health; Bethesda, Maryland; ¹⁹University of British Columbia, British Columbia Children's Hospital, Vancouver, British Columbia, Canada; ²⁰University of Minnesota, Minneapolis, Minnesota

Correspondence and reprint requests: Steven Z. Pavletic, MD, Graft-versus-Host and Autoimmunity Unit, Experimental Transplantation and Immunology Branch, National Cancer Institute, 9000 Rockville Pike, Bethesda, MD 20892-1203 (e-mail: pavletis@mail.nih.gov).

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ABSTRACT

The lack of standardized criteria for quantitative measurement of therapeutic response in clinical trials poses a major obstacle for the development of new agents in chronic graft-versus-host disease (GVHD). This consensus document was developed to address several objectives for response criteria to be used in chronic GVHD-related clinical trials. The proposed measures should be practical for use both by transplantation and nontransplantation medical providers, adaptable for use in adults and in children, and focused on the most important chronic GVHD manifestations. The measures should also give preference to quantitative, rather than semiquantitative, measures; capture information regarding signs, symptoms, and function separately from each other; and use validated scales whenever possible to demonstrate improved patient outcomes and meet requirements for regulatory approval of novel agents. Based on these criteria, we propose a set of measures to be considered for use in clinical trials, and forms for data collection are provided (<http://www.asbmt.org/GvHDForms>). Measures should be made at 3-month intervals and whenever major changes are made in treatment. Provisional definitions of complete response, partial response, and progression are proposed for each organ and for overall outcomes. The proposed response criteria are based on current expert consensus

opinion and are intended to improve consistency in the conduct and reporting of chronic GVHD trials, but their use remains to be demonstrated in practice.

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KEY WORDS

Chronic graft-versus-host disease • Allogeneic cell transplantation • Response criteria • Consensus

INTRODUCTION

Overall survival or survival to permanent resolution of chronic graft-versus-host disease (GVHD) and discontinuation of systemic immunosuppression are long-term clinical outcomes that are accepted major end points in chronic GVHD clinical trials [1-3], but these long-term outcomes are not suitable for early-phase studies. Qualitative assessments of chronic GVHD manifestations can guide clinical decisions but are not adequate for measuring outcomes in clinical trials. To accelerate development of novel therapeutic agents in chronic GVHD, quantitative research tools are needed to measure short-term responses to treatment and to predict long-term clinical benefit.

The lack of standardized quantitative response criteria poses one of the major obstacles in pursuing therapeutic trials for chronic GVHD [4]. No generally accepted, much less validated, quantitative criteria for organ-specific or overall responses have been developed previously. The definitions of response typically used in previous studies have been global and qualitative in nature, with considerable variability from one study to the next (extensively reviewed by Gorgun Akpek in Attachment 1 at <http://www.asbmt.org/GvHDForms>). In addition, methods have not been developed to account for the distinction between reversible disease activity and irreversible damage.

Because no currently available database has information from patients with chronic GVHD at a sufficient level of detail, retrospective methods could not be used to identify clinical characteristics that are sensitive to change and predictive for major outcomes. The Working Group began by reviewing instruments currently used by hematopoietic stem cell transplantation physicians at Johns Hopkins, Children's Oncology Group, Fred Hutchinson Cancer Research Center, Harvard University, University of Minnesota, and National Institutes of Health. The Working Group also included specialists from other fields, including rheumatology and gastroenterology, to benefit from their experiences in developing and using chronic disease activity indices and response criteria in clinical trials [5-8].

This document is based on a broad consensus of experts and on the use of the best available data. These 2005 recommendations are intended to advance standards of chronic GVHD therapeutic trials, but they remain provisional and will need to be validated and

refined according to data emerging from prospective studies. The Working Group could not entirely resolve certain intrinsic tensions between divergent goals. On the one hand, the assessments should be as simple as possible to facilitate their use by clinicians outside the field of hematopoietic cell transplantation, but on the other hand, the assessments should contain as much information as possible to support research. The former goal would require immediate item reduction and enforcement of consistency based on expert opinion, whereas the latter goal would encourage further exploration, with deferral of item reduction until data are available. For certain organs, the Working Group could not identify quantitative measures that would be suitable for use in clinical trials, even though qualitative assessments can be used for clinical management. In the end, the Working Group proposed a broad set of assessment measures that should be feasible in most academic settings, although some simplification might be needed if the assessments are to be used by medical providers outside the field of hematopoietic cell transplantation.

The differences between this document and the Diagnosis and Staging document should be noted [9]. Although there is appearance of some overlap, characteristics that could help establish the diagnosis of chronic GVHD or to assess the severity of chronic GVHD at a single time point might not serve as the most appropriate or sensitive measures for chronic GVHD disease activity. Conversely, a sensitive measure of chronic GVHD response might not necessarily serve as an appropriate diagnostic and staging tool.

PURPOSE OF THIS DOCUMENT

This document summarizes proposed measures and criteria for assessing outcomes in clinical trials involving patients with chronic GVHD. The measures and criteria do not necessarily reflect practices that might apply to routine patient care or to trials with limited resources. The measures and response criteria were developed to meet certain requirements.

1. *The instruments should be easy to use by both transplantation and nontransplantation care providers and should be limited to testing methods that are available in the outpatient setting.*
2. *The criteria should be adaptable for use in adults and in children.*

3. The instrument should focus on the most important and most common manifestations of chronic GVHD and should not be designed to characterize all possible clinical manifestations.
4. Development should focus on quantitative measures as much as possible.
5. Measurements of symptoms, signs, global ratings, function, quality of life, or performance status should be made separately, and scales with established psychometric characteristics and desirable measurement properties should be used whenever possible [10,11].
6. With appropriate refinements and reliability and validation assessments, these tools should be suitable for use in clinical trials where the goals are to improve patient outcomes or to obtain regulatory approval.

The Working Group had 3 additional goals: (1) to propose provisional definitions of complete response, partial response, and disease progression for each organ and for overall response; (2) to suggest appropriate strategies for using short-term end points in therapeutic clinical trials; and (3) to outline future research directions.

SUMMARY OF RECOMMENDATIONS

1. Proposed chronic GVHD-specific core measures include:
 - A. Clinician- or patient-assessed signs and symptoms.
 - B. The chronic GVHD symptom scale by Lee et al [12].
 - C. The clinician- or patient-reported global rating scales (Table 1) [12-14].

To facilitate validation studies, continuous data should be recorded as such and should not be reduced to prespecified categories.
2. Proposed chronic GVHD nonspecific ancillary measures for adults include:
 - A. Measurement of grip strength [15-17] and 2-minute walk time [18].

- B. Patient-reported Human Activity Profile (HAP) questionnaire [19].
- C. Clinician-assessed Karnofsky performance status.
- D. The SF-36 version 2 questionnaire [20,21] and FACT-BMT for quality-of-life assessments (Table 1) [22].

The ancillary chronic GVHD nonspecific measures are optional and should not be used as primary end points in chronic GVHD trials.

3. Age-appropriate modifications of existing measures should be used and explored in children with chronic GVHD [23-29].
4. Definition of response involves a comparison of chronic GVHD activity at two different time points. Provisional definitions of complete response, partial response, and progression are offered for each organ and for overall outcomes. Simple forms to be used for clinician and patient assessments are provided in Appendices A and B at <http://www.asbmt.org/GvHDForms> (Forms A and B). In each specific trial, irreversible baseline organ damage may be defined initially and then excluded in response assessments.
5. Measures should be made at 3-month intervals and whenever a major change is made in treatment. Permanent discontinuation of systemic immunosuppressive treatment indicates a durable response.
6. Further assistance from subspecialists will be needed to develop organ- or site-specific measures that could improve the sensitivity of chronic GVHD assessments. Specific organ or site assessments discussed by the Working Group include the following:
 - A. Skin: skin-specific scoring systems [30], durometer [30-32], biopsy [31], or imaging (ultrasound, magnetic resonance imaging) [33,34].
 - B. Eyes: corneal staining grading [35], conjunctival grading [36], ocular surface disease index [37].

Table 1. Proposed Measures for Assessing Responses in Chronic GVHD Trials

Measure	Clinician Assessed	Patient Reported
I. Chronic GVHD-specific core measures		
Signs	Organ-specific measures	N/A
Symptoms	Clinician-assessed symptoms	Patient-reported symptoms Lee symptom scale [12]
Global rating	Mild-moderate-severe [12] 0-10 severity scale [13] 7-point change scale [14]	Mild-moderate-severe [12] 0-10 severity scale [13] 7-point change scale [14]
II. Chronic GVHD-nonspecific ancillary measures		
Function	Grip strength [15-17] 2-min walk time [18]	HAP [19] ASK in children [23-25]
Performance status	Karnofsky or Lansky [26]	
Quality of life		SF-36v.2 [20,21] or FACT-BMT [22] in adults CHRIs in children [27-29]

ASK indicates Activities Scale for Kids; GVHD, graft-versus-host disease; N/A, not applicable; HAP, Human Activity Profile; CHRIS, Child Health Ratings Inventories.

- C. Oral: Oral Mucositis Rating Scale [38].
 D. Vulvar-vaginal: organ-specific staging [39,40].
 E. Function: range of motion, limb volume, fatigue severity scale [41-43].

PROPOSED MEASURES OF CHRONIC GVHD RESPONSE ASSESSMENTS

The Working Group distinguished between chronic GVHD-specific core measures that directly measure organ-specific manifestations of chronic GVHD and nonspecific ancillary measures, which could reflect the overall impact of chronic GVHD and other illness on functioning or quality of life (Table 1). In future studies, these measures should be evaluated for construct validity (for Glossary see Attachment 2 at: <http://www.asbmt.org/GvHDForms>) and potential item reduction. In a feasibility study, 8 clinicians who had never previously used the assessment forms evaluated 4 adults with chronic GVHD [44]. The median time for each clinician evaluation was 36 minutes, and the median time needed to complete the panel of patient self-report items was 14 minutes. Results of this evaluation offered preliminary evidence of reliability, feasibility, and acceptability of the newly proposed measures.

PROPOSED CLINICIAN-ASSESSED AND PATIENT-REPORTED CHRONIC GVHD-SPECIFIC MEASURES

The following sections describe the recommended clinician-assessed and patient-reported chronic GVHD-specific measures (Table 2). Specific pediatric considerations for such situations are highlighted where appropriate. For the assessment of symptoms in younger children, depending on the child's development, assistance can be provided by the health care provider or the parent. The Working Group also recommends formal in-person training for all assessments to minimize intraobserver and interobserver variability. Instructional manual and slide set to assist with such training are available at <http://www.asbmt.org/GvHDForms>.

Organ-specific Assessments

Skin and skin appendages. Skin is the most frequently affected organ in chronic GVHD, and manifestations are highly variable. Skin assessments are structured to reflect 4 anatomic levels of skin involvement: (1) erythematous rash (epidermal involvement); (2) movable sclerosis (dermal involvement); (3) non-moveable sclerosis, hidebound skin, or involvement of

Table 2. Proposed Clinician-Assessed and Patient-Reported Chronic GVHD-Specific Measures

Component	Items Assessed	Measure	Assessor
Skin	Erythematous rash of any sort	% Body surface area	C
	Movable sclerosis	0%-100% For each feature	C
	Nonmoveable sclerosis or subcutaneous sclerosis/fasciitis	By using rule of nines	C
	Ulcers	Largest dimension (cm) of the largest ulcer	C
Eyes	Pruritus or itching	0-10 Scale	P
	Bilateral Schirmer's tear test scores without anesthesia	Mean of both eyes, mm	C
Mouth	Main ocular symptom at the time of the visit	0-10 Scale	P
	Erythema	Total score 0-15	C
	Lichen-type hyperkeratosis		C
	Ulcerations		C
Hematology	Mucoceles		C
	Symptoms of oral pain, dryness, sensitivity	0-10 Scale	P
	Platelet count	Number/ μ L	C
GI	Eosinophils	Percent	C
	Upper GI symptoms	0-3 Score	C
	Esophageal symptoms	0-3 Score	C
Liver	Diarrhea	0-3 Score	C
	Total serum bilirubin	mg/dL	C
Lungs	ALT, alkaline phosphatase	U/L	C
	Bronchiolitis obliterans syndrome	FEV ₁ , DLCO	C
Chronic GVHD symptom scale [12]	30 items, 7 subscales, 1 summary scale	0-100	P
Global activity rating	Severity of chronic GVHD symptoms	0-10	C/P
	Perception of change	+3 to -3	C/P
	Overall severity of chronic GVHD	Mild - moderate-severe	C/P

ALT indicate alanine aminotransferase; C, assessed by the clinician; DLCO, diffusion lung capacity for carbon monoxide; FEV₁, forced expiratory volume in the first second; GI, gastrointestinal; GVHD, graft-versus-host disease; P, reported by the patient.

Vulvar-vaginal symptoms (yes or no) and patient weight should be recorded at each visit.

Range of motion of the most affected joints should be recorded depending on the availability of a physical therapist.

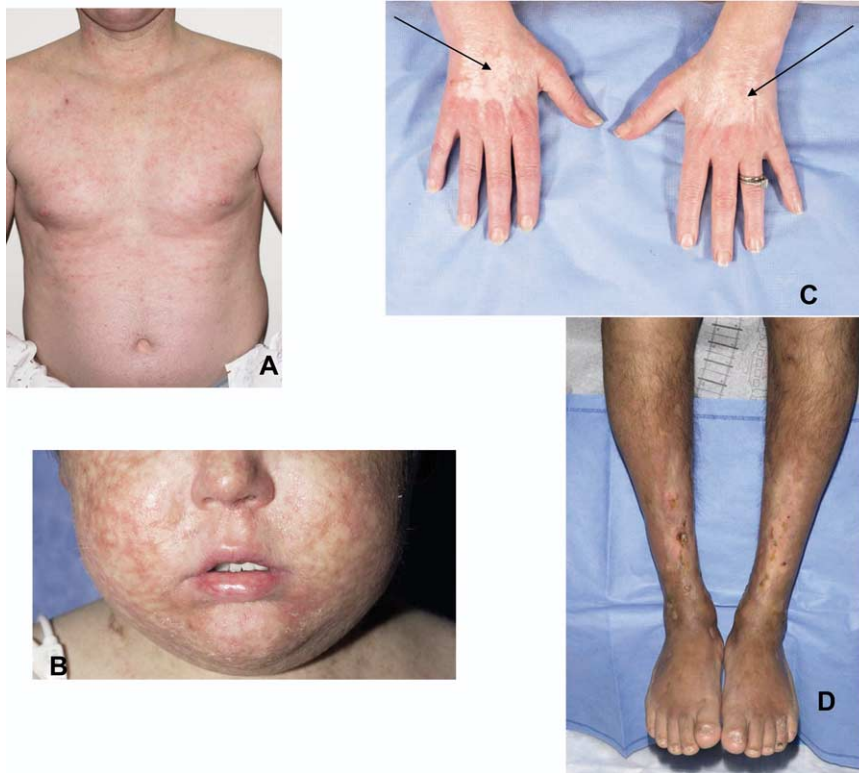


Figure 1. Skin manifestations assessed for response in chronic GVHD. A, Erythematous papular rash. B, Erythematous rash with papules and small scaly plaques. C, Dermal sclerosis. Skin is thickened, with decreased mobility to pinching but without adherence to underlying tissues. D, Subcutaneous sclerosis. Skin is hidebound, fixed to underlying tissues and cannot be pinched. Ulcers are present.

subcutaneous tissue and fascia (subcutaneous involvement); and (4) ulceration (full thickness loss of epidermal tissue) (Figure 1). Abnormalities for the first 3 points are each assessed separately according to the percent of body surface area (BSA) involved as estimated by the rule of nines for adults. A worksheet for recording the BSA involved for each of 8 skin regions is provided at: <http://www.asbmt.org/GvHDForms> (Attachment 3). Ulcer size is assessed by measuring the largest diameter of the largest ulcer.

The term “erythematous rash of any sort” is used as an inclusive reference to the many superficial skin eruptions of chronic cutaneous GVHD including papular, lichen planus-like, papulosquamous, poikiloderma, and keratosis pilaris-like rashes. The term “lichenoid” is not used, because this is a histopathologic diagnosis, not a clinical descriptive term.

Likewise, the term “sclerosis” or “sclerotic” is used to represent the general category of cutaneous GVHD findings associated with skin fibrosis, and to avoid confusion with the autoimmune disorder scleroderma. Superficial sclerosis (moveable) includes both lichen sclerosus-like and morphea-like lesions. Deep sclerosis includes diffuse, immovable (hidebound) sclerosis involving a wide area of skin, fibrosis of subcutaneous fat septae (rippling), and fasciitis (groove sign). Sclerotic skin manifestations may be as variable as the

superficial form of the disease and are difficult to measure reliably. Sclerotic changes respond slowly to therapy and progression or regression of sclerotic lesions ideally should be assessed not only according to the total surface area involved but also according to the depth of involvement at any given site.

Because quantitative methods to measure the depth of sclerotic involvement are not available in a general oncology practice, these changes have been described in more qualitative terms related to thickening, pliability, adherence to underlying tissues, or changes in joint mobility. No validated scale exists for assessing sclerotic skin changes of chronic GVHD. Measures such as the Rodnan score for assessment of systemic sclerosis might be helpful for clinical evaluation of chronic GVHD, but this scale does not measure lichen sclerosus-like changes, subcutaneous involvement without overlying skin thickening, or fascial involvement. For this reason, the Rodnan score is not suitable for use in clinical trials. More sophisticated skin-specific scores are being developed for use by trained assessors in selected clinical trials (R. Knobler, MD, and H. Greinix, MD, oral communication, December 2005). There is an urgent need for the development of more quantifiable and reproducible measurements or imaging methods that could be used in patients with sclerotic skin manifestations of chronic GVHD [30-34].

Pigmentary changes do not indicate activity in chronic GVHD disease per se. Moreover, changes in pigmentation occur gradually and are perceptible only across long time intervals. Nonetheless, these changes should be recorded in the assessment forms, as described in the Diagnosis and Staging document [9], because they indicate the extent of previous skin involvement. Individuals who assess chronic GVHD of the skin should consult a picture atlas that is available for training and standardization (<http://www.asbmt.org/GvHDForms>).

The patient symptom intensity self-report profile includes the most severe itching during the past week, rated according to a 1-to-10 scale, because itching is the most frequent cutaneous symptom of chronic GVHD.

The rule of nines as an estimate of BSA involvement is intended for use in adults and is less accurate in children, particularly young children. For the sake of simplicity, we recommend using the rule of nines for all children, except for those younger than 1 year. A BSA grid for children younger than 1 year can be found at: <http://www.asbmt.org/GvHDForms> (Attachment 4).

Eyes. Dry eyes reflect either lacrimal dysfunction or destruction. The primary measure of lacrimal gland function in chronic GVHD is the Schirmer's test (to be performed without anesthesia) for each eye separately, as recommended by the Sjögren's syndrome consensus group [45]. Objective improvement would not be expected in cases where dry eyes and abnormal Schirmer's test result from complete lacrimal destruction. Instructions for administration of the Schirmer's test are provided with the instructional manual at: <http://www.asbmt.org/GvHDForms>.

The patient symptom intensity self-report profile includes the chief eye complaint rated according to a 1-to-10 scale for peak severity during the past week. The complaint can change from visit to visit, but only one chief eye complaint is graded. This method is simple to use but may impose undesirable limitations in patients with multiple complaints. In addition, ocular symptoms in patients with chronic GVHD can have causes other than chronic GVHD.

Schirmer's test without anesthesia is not recommended for children younger than 9 years, and evaluation by an ophthalmologist may be needed for objective scoring in younger children.

Mouth. Mouth assessments are conducted by using the newly proposed modification of the Schubert Oral Mucositis Rating Scale that scores oral surfaces from 0 to 15, with higher scores indicating more severe involvement. The 4 chronic GVHD manifestations assessed in this scale include: (1) mucosal erythema (0-3) grading based on the color intensity; (2) lichen-type hyperkeratosis (percent of oral surface area); (3) ulcerations (percent of oral surface area); and (4) presence of mucoceles (total number) (Figure 2). Instructions

for these assessments and a photo dictionary are provided in the instructional manual on the World Wide Web: <http://www.asbmt.org/GvHDForms>.

The patient self-report symptom intensity profile includes dry mouth (subjective decrease in oral wetness), mouth pain in the absence of stimulation, and mouth sensitivity (irritation resulting from normally tolerated spices, foods, liquids, or flavors), each rated according to a 1-to-10 scale for peak severity during the past week.

Hematopoietic. Parameters to be evaluated for response assessments are absolute platelet count [46] and absolute eosinophil count [47]. Total white count and percent eosinophils are also recorded on the form at the time of the clinic visit.

Gastrointestinal tract. Gastrointestinal (GI) symptoms are difficult to measure in the outpatient setting. For this reason, GI symptoms during the preceding week are graded not through patient self-report forms but through interview by the examining clinician according to 0-to-3 severity scales. For upper GI symptoms of early satiety, anorexia, nausea, and vomiting, a score of 1 indicates mild, occasional symptoms, with little reduction in oral intake. A score of 2 indicates moderate, intermittent symptoms, with some reduction in oral intake, and a score of 3 indicates more severe or persistent symptoms throughout the day, with marked reduction in oral intake on most days. For esophageal symptoms of dysphagia or odynophagia, a score of 1 indicates occasionally difficult or painful swallowing of solid foods or pills. A score of 2 indicates intermittent dysphagia or odynophagia with solid foods and pills, but not for liquids or soft foods, and a score of 3 indicates dysphagia or odynophagia for almost all oral intakes on most days. Finally, for lower GI symptoms, a score of 1 indicates occasional loose or liquid stools, on some days. A score of 2 indicates intermittent loose or liquid stools throughout the day without requiring intervention to prevent or correct volume depletion, and a score of 3 indicates voluminous diarrhea requiring intervention to prevent or correct volume depletion.

Patients with chronic GVHD often have weight loss that is not always explained by GI symptoms [48]. Although the exact relationship between weight loss and chronic GVHD activity is not clear, patient weight should be recorded at each scheduled evaluation, given the simplicity of this measure and its potential importance for monitoring the success of therapy.

Liver. Liver injury should be assessed according to the most recent laboratory results for total serum bilirubin (mg/dL), alanine aminotransferase (U/L), and alkaline phosphatase (U/L). Laboratory upper limits of normal should also be recorded.

Lung. Measures that can be used to evaluate the response of bronchiolitis obliterans syndrome (BOS)

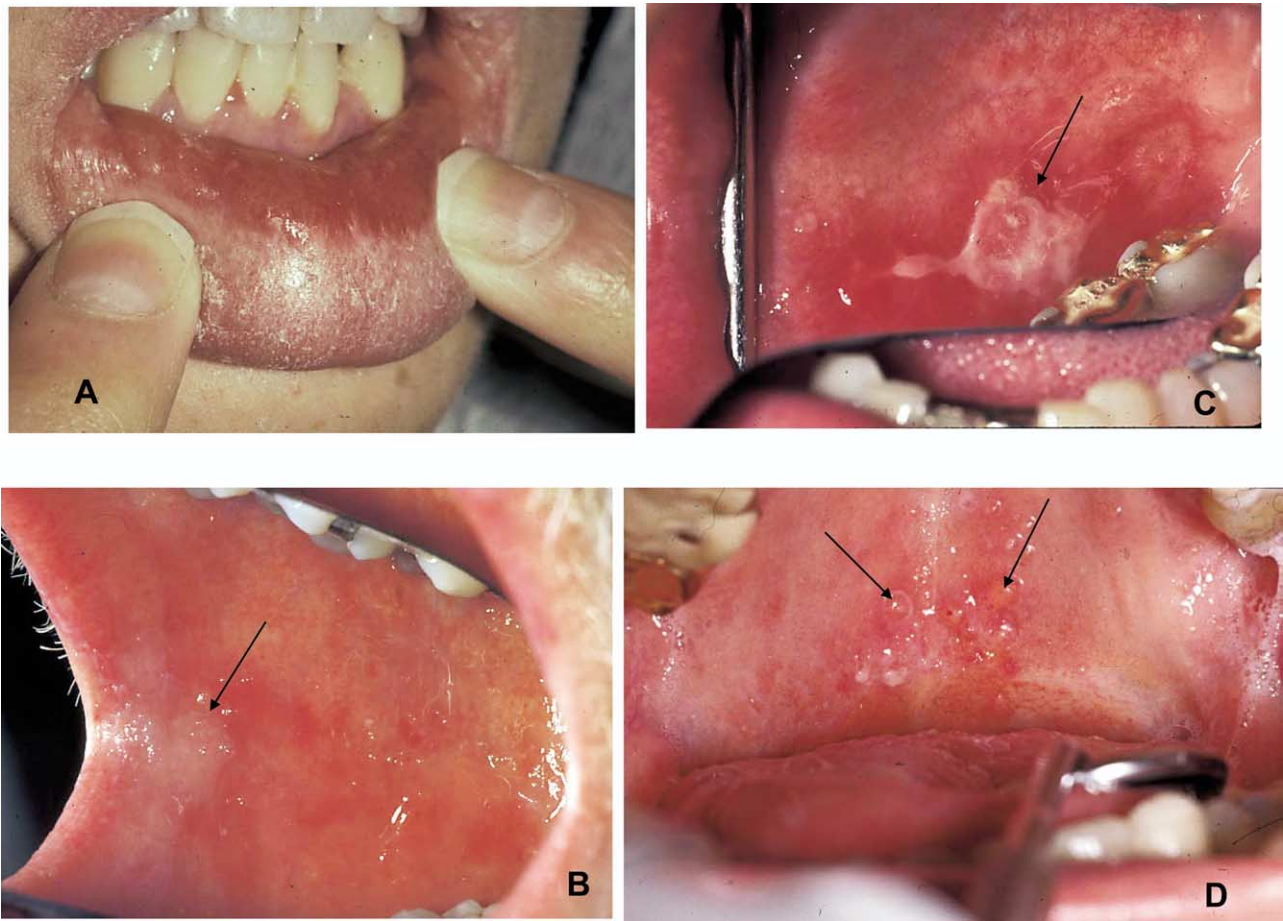


Figure 2. Oral manifestations assessed for response in chronic GVHD. A, Moderate erythema of vermilion lip. Labial mucosa shows severe erythema. B, Area of sheetlike lichenoid hyperkeratosis is present inside commissure. C, Ulcer with pseudomembranous fibrin exudates surrounded by severe erythema. D, Numerous vesicle-like mucocèles are seen at center of the palate, with patches of lichenoid hyperkeratosis and moderate erythematous changes.

after therapy are forced expiratory volume in the first second (FEV₁) and single breath diffusion lung capacity for carbon monoxide (DLCO) adjusted for hemoglobin, both of which are included in standard pulmonary function testing [49]. These two parameters are also included as components of the lung function score (LFS) that was recently developed as a predictor of respiratory failure and mortality after allogeneic hematopoietic stem cell transplantation [50]. A modified LFS is proposed as a simple measure of changes in the lung function in patients with BOS (see Table 3). Pulmonary function tests should be performed in children who are older than 5 years.

The LFS is computed according to FEV₁ and DLCO measurements compromise (>80% of predicted = 1, 70%-79% = 2, 60%-69% = 3, 50%-59% = 4, 40%-49% = 5, <40% = 6). The scores for FEV₁ and DLCO are then added together, and the sum is reduced to an overall category according to Table 3.

It is important to emphasize that the LFS has never been used in chronic GVHD response assessments, and its exact role in this setting needs to be

determined. To allow validation in trials, absolute values of both FEV₁ and DLCO should be recorded on the data collection forms.

Vulva and vagina. Women should be asked specific questions relating to vulvar and vaginal symptoms, such as burning, pain, discomfort, or dyspareunia. Patients who report problems should be referred to a gynecologist. Because such symptoms could be caused by conditions other than chronic GVHD, and because proper evaluation requires a specialist examination, this information should be recorded but not scored for response assessment. Academic gynecologists interested in chronic GVHD are developing precise vulvovaginal assessment scales. These scales will be useful

Table 3. Categories of the Lung Function Score

Category	Lung Function	LFS
I	Normal	2
II	Mild decrease	3-5
III	Moderate decrease	6-9
IV	Severe decrease	10-12

in selected trials where vulvar and vaginal changes are the primary end points of interest [39,40].

Musculoskeletal connective tissue. Active-assisted range of joint motion could potentially serve as a very useful objective measure of chronic GVHD tissue response in patients with sclerotic changes involving large joints or the trunk. The main limitation of this tool, however, is the need for an adequately trained professional (usually a physical therapist) who can conduct the range-of-motion measurements in a standardized and reproducible fashion. If such a trained professional is available, pertinent range-of-motion measurements should be recorded sequentially, and for this purpose, trained clinicians should also be able to make serial measurements of selected sentinel joints for routine assessment purposes. Normal levels are available for adults and for children [51].

Chronic GVHD Symptoms

Lee et al [12] developed a symptom scale designed for individuals with chronic GVHD. The questionnaire asks respondents to indicate the degree of bother that they experienced during the past 4 weeks as a result of symptoms in 7 domains potentially affected by chronic GVHD (skin, eyes and mouth, breathing, eating and digestion, muscles and joints, energy, emotional distress). Published evidence supports its validity, reliability, and sensitivity to chronic GVHD severity. Items in this symptom scale can be reported in approximately 5 minutes.

The Lee chronic GVHD symptom scale has been tested only in individuals older than 18 years. Given its face validity and other desirable properties, however, this scale could be used for assessment of chronic GVHD in pediatric patients using either child or parent report, after appropriate modification and psychometric evaluation [52]. Information for the chronic GVHD symptom scale could be obtained by self-report from adolescents older than 12 years. For children who are 8 to 12 years of age, data should be obtained with the assistance of parents and the health care provider.

The Lee scale measures symptom bother as distinguished from symptom intensity, which is reported on the forms in Appendix B [53]. The degree to which patients report that they are bothered by a symptom represents a global assessment incorporating not only the intensity of the symptom and its frequency, but also the degree to which it causes emotional disturbance or interferes with functioning. The Lee scale complements the information regarding the intensity of chronic GVHD symptoms. For example, oral sensitivity may be severe, but patients may report that they are not bothered or distressed by this symptom. By contrast, skin itching may not be very intense or frequent but may cause great distress. Research is

needed to determine the relationships between symptom intensity, frequency, and distress or bother in patients with chronic GVHD and to examine the degree to which these are distinct dimensions of the symptom experience.

Clinician- and Patient-Reported Global Ratings

Clinician perceptions. Physicians, nurse practitioners, or physician assistants should provide an assessment of current overall chronic GVHD severity on a 4-point scale (none, mild, moderate, severe) [12] and they can also provide an assessment of current overall chronic GVHD severity on an 11-point numeric scale (0 indicates no GVHD manifestations; 10 indicates most severe chronic GVHD symptoms possible). The categories of mild, moderate, and severe have been used in previous studies for patient and clinician assessment, where they were undefined but showed good prognostic characteristics [12,54]. Clinicians should also provide their assessments of patient chronic GVHD changes during the past month scored on a 7-point scale (very much better, moderately better, a little better, about the same, a little worse, moderately worse, very much worse) [14].

Patient perceptions. Similarly, at each patient self-assessment, patients should score their perceptions of overall chronic GVHD severity, overall severity of symptoms, and change in symptom severity compared with 1 month ago, using the same response options used by clinicians.

The exact role of global scales in chronic GVHD response assessments and their appropriate use as outcome measures in clinical trials remains to be determined. These scales could be sensitive to qualitative changes that might otherwise escape detection if the assessments were limited to quantitative measures.

PROPOSED CHRONIC GVHD NONSPECIFIC MEASURES

Nonspecific measures of function and patient-reported outcomes related to functional status and health-related quality of life could potentially offer additive objective and subjective data regarding the effects of chronic GVHD and its therapy. The GVHD nonspecific measures listed for consideration in Table 1 assess different dimensions of the patient experience. Selection of these instruments was based on the credibility and relevancy of their measurement properties (reliability, validity, responsiveness) and the availability of normative data to facilitate interpretation. Instruments that use self-report methods as opposed to interview-assisted reporting will promote feasibility in clinical trials, and the number of instruments was circumscribed to limit the burden on respondents. Consideration was also given to the availability of detailed instructions, procedure manuals,

coding algorithms and scoring systems, and background information regarding the conceptual and measurement properties of the instrument. The potential role of these nonspecific measures as outcomes in chronic GVHD therapeutic clinical trials needs to be determined in future research.

Functional Status

For an extremely complex multisystem disease such as chronic GVHD, objective measures of physical performance and patient-reported measures of functional status could represent important surrogate outcomes that might be more informative than the measures described above for assessing outcome in some situations (eg, advanced skin sclerosis). At the very least, measures of functional status can provide corroborative evidence of important changes after therapy. In other patient populations with chronic diseases [55-57], such outcomes have been extensively applied, and population norms for both physical performance measures and self-reported functional status are available. Because the use of functional end points in chronic GVHD assessment has not been extensively tested, and because these measures do not directly assess chronic GVHD manifestations, functional status outcomes can be used only as optional secondary end points in chronic GVHD trials until further information is available.

Proposed objective measures of physical performance include grip strength [15-17] measured using a hydraulic dynamometer (measured in pounds of pressure) and the 2-minute walk distance (measured as total distance in feet walked in 2 minutes) [18]. Although the measurement properties for the 2-minute walk distance have been less thoroughly examined than those of the 6-minute walk distance, the 2-minute walk may be a more feasible and efficient measure of performance in patients with chronic GVHD. Studies support the construct validity and responsiveness to change characteristics of the 2-minute walk distance [58,59]. Age-matched norms for walk time and grip strength are available for adults and for children. These simple instruments might not be available in the typical oncology clinic, but they can be obtained from rehabilitation medicine departments or purchased (eg, at: http://www.rehaboutlet.com/grip_hand_dynamometer.htm).

HAP. Recommended patient-reported measures of functional status include the HAP questionnaire (for adults) and the Activities Scale for Kids questionnaire (for children age 5-15 years) [19,23-25]. The HAP is a measure of physical activity. The 94 questions are ranked hierarchically in ascending order according to the metabolic equivalents of oxygen consumption required to perform each activity [19]. The HAP, therefore, provides a survey of the activities the

patient performs independently across a wide range of metabolic demand, beginning with getting out of bed, bathing, dressing, walking using public transit, performing a series of progressively more physically demanding household chores, and ending with running or jogging 3 miles in 30 minutes or less. The recommended corollary instrument to measure self-reported function in children is the Activities Scale for Kids [23-25].

Performance scales. The Karnofsky Performance Scale is commonly used in clinical assessments of chronic GVHD and has prognostic value for survival [60]. Whether a clinician assessment that combines performance, health status, and impairment is a valid, reliable, or sensitive tool to gauge response after therapy for chronic GVHD remains to be determined. Performance scores should nonetheless be recorded as part of each assessment. Lansky Play Performance Scale scores should be recorded for children younger than 16 years [26].

Self-Reported Health-Related Quality of Life

The effects of chronic GVHD and its treatment on general physical and emotional health and quality of life are other patient-reported outcomes that may be responsive to change as a result of chronic GVHD therapy [61]. The Medical Outcomes Study Short Form 36-item Questionnaire version 2* is a measure that has had wide application and is well accepted as measure of self-reported general health and the degree to which health impairments interfere with activities of daily living and role function [21,62]. The Functional Assessment of Chronic Illness Therapy is an oncology-specific quality-of-life instrument that has well-developed psychometric properties, and population norms for healthy individuals and those with both mild and more severe chronic illnesses. An additional 18-item disease-specific module evaluates concerns common to patients who have had stem cell transplantation (FACT-BMT)* [22]. These instruments are appropriate for patients older than 18 years. In pediatric patients, the Child Health Ratings Inventories* generic core and Disease-Specific Impairment Inventory-HSCT*, a hematopoietic cell transplantation-specific module, could serve as a surrogate for FACT-BMT [27-29].

Cross-sectional studies have shown that chronic GVHD has an adverse effect on quality of life [63], but the role of quality of life as a measure of response to therapy or as a predictor of long-term outcome remains to be defined. Patient-reported quality-of-life measures cannot replace quantitative measures of chronic GVHD activity in clinical trials. Patient-reported items should be selected to address specific questions and should have relevance for chronic GVHD. Each instrument should be considered not

only for the information that it might provide in its own right but also for the information that it might add in the context of other instruments to be used in assessments. Hence, investigators should be aware of similarities and differences between instruments when making decisions about their use in clinical trials. Investigators should take care not to impose an excessive burden of self-report items on those who are participating in clinical trials. A table comparing above-discussed chronic GVHD-specific and the optional patient-reported nonspecific measures is provided at: <http://www.asbmt.org/GvHDForms> (Attachment 5). The recommendation to use these instruments does not imply permission for their use in clinical trials. Investigators should follow the procedure established by the organizations that hold copyright for each instrument (see Attachment 5).

CHRONIC GVHD DATA COLLECTION FORMS

Appendices A and B (<http://www.asbmt.org/GvHDForms> [Forms A and B]) show data collection forms for the recommended clinician-assessed and patient-reported measures. In clinical trials, data should be submitted to the study coordinating center for further calculations, processing, and interpretation of responses. It is not necessary to include recommended measures in every trial, and judgment must be used in deciding which items will best suit the needs of each study. In all studies, the measures to be made and the timing of the measures must be specified.

PROVISIONAL CRITERIA FOR DEFINITION OF RESPONSE

Protocols must specify the times when response will be assessed, and the requirement for durability of response (see forthcoming Design of Clinical Trials Working Group report). Permanent discontinuation of systemic immunosuppressive treatment indicates a durable response.

Certain changes such as dry eyes, esophageal stricture, bronchiolitis obliterans, or advanced sclerotic skin lesions may be considered irreversible and may be excluded from consideration for assessments of complete or partial response, if specified by the protocol.

To assess response, disease manifestations at two different time points must be compared, and a judgment must be made as to whether the magnitude of any change qualifies as clinical improvement or clinical deterioration. The magnitude of change required for clinical improvement or deterioration should reflect genuine clinical meaning, and the criteria should be developed and standardized as much as possible. This standardization may be relatively easy to establish for manifestations that can be measured quantita-

tively with little day-to-day variation but will be more difficult to establish for manifestations that can be measured only in more qualitative ways.

The statistician should be always be included early in the development of the trial design and should help to select the analyses that best fit the types of measures being collected. Because no criteria for defining meaningful improvement or clinical benefit have been validated for measures of chronic GVHD, the results of trials should include both the categorical outcomes defined below and the average change from baseline for each parametric measure. Protocols should specify whether change is to be calculated according to percent of full scale or percent of baseline. Analysis of percent changes is particularly needed for the interpretation of smaller early drug-development trials.

Pending appropriate validation studies, the Working Group proposes the following consensus definitions of complete response, partial response, and progression. The complete and partial response categories apply only to organs that have measurable and reversible GVHD-related abnormalities at baseline. For certain organs and measures, however, chronic GVHD sequelae can reflect damage that is not reversible. Some obvious examples of this problem are chronic dry eyes, esophageal stricture, bronchiolitis obliterans, or advanced skin sclerosis or contractures. For these manifestations, the category of complete organ response may not apply if protocols prespecify any such exclusion. The progression category applies to all organs.

Objective Measures of GVHD Activity

Complete organ response. The term “complete organ response” indicates resolution of all reversible manifestations related to chronic GVHD in a specific organ.

Partial organ response. The proposed general guideline for defining partial response in specific organ requires at least 50% improvement in the scale used to measure disease manifestations related to chronic GVHD. This guideline was selected as unequivocally indicating genuine clinical benefit. The criterion of 50% improvement requires some adjustment in cases where the extent of abnormality at the baseline measurement is low. For example, there would be no question that a 50% decrease in rash from 80% of BSA to 40% represents genuine clinical improvement. On the other hand, the same 50% decrease from 5% of BSA to 2.5% would represent a much less compelling clinical improvement. For this reason, when the extent of abnormality at the baseline measurement is lower than the midpoint on the scale, the minimum criterion for response should be defined as percentage (eg, 25%) of the full scale as opposed to a percentage of the starting value. To be consistent, if the extent of abnormality at the baseline measurement

is lower than the minimum percent of full-scale change needed to define a partial response (eg, 25% of the full scale), then the only possible response would be a complete response.

Organ progression. Criteria for progression in each organ must be defined, because the overall category of partial response requires the absence of progression in any organ (see below). For an organ affected by chronic GVHD at the baseline evaluation, the proposed general guideline for defining progression specifies an absolute increase of at least 25% in the scale used to measure disease manifestations related to chronic GVHD. Progression cannot be scored for manifestations with baseline values that are within 25% of the full-scale value. When baseline measures of chronic GVHD severity are 50% to 75% of full scale at baseline, the criteria for improvement require more than a 50% change from baseline (which produces more than a 25% of full-scale change), whereas a 25% of full-scale change is sufficient for progression. This asymmetry in the minimal criteria for improvement and progression is intended to ensure a high level of confidence that any improvement is clinically meaningful and to ensure early detection of any deterioration.

Proposed guidelines for calculating partial response and progression and instructions for use by study coordinating centers are available on the World Wide Web at: <http://www.asbmt.org/GvHDForms.htm> (Appendices C and D). The criteria proposed in these guidelines are admittedly arbitrary, because in most cases, they have never been validated for patients with chronic GVHD, and the distribution of baseline scores is unknown. For these reasons, the proposed criteria are provisional and subject to change with further clinical experience. Also, depending on the stringency of response definitions required by the specific study, these general guidelines could be modified to fit the needs of a particular protocol. Because the criteria are subject to change, we strongly recommend that data report forms should always record the actual numeric values for any measurement.

Limitations in measurement of organ responses. The response criteria in Appendix C do not account for qualitative changes. Clinical experience indicates that clinically important qualitative improvement often occurs before improvement in the measures summarized in Appendix C. For this reason, the response criteria in Appendix C should not be used as the primary guide for clinical decisions. Certain organs are not considered in Appendix C because quantitative assessments are not feasible. The response criteria also do not account for the prior trajectory of abnormalities. For example, stable disease might be considered a response when the prior trajectory was clear progression, as indicated, for example, by serial pulmonary function tests. Stable disease after prior improvement

could not be considered a favorable outcome, and stable disease after prior stability cannot be considered a response.

Standardized response criteria for BOS associated with chronic GVHD have never been investigated. The hallmark of response to therapy for BOS is stabilization of lung function with no further decrease in FEV₁ during a 3-month period. A few cases of improved FEV₁ after therapy for BOS have been reported, but these outcomes could reflect disease misclassification or very early treatment.

Definitions of overall response. Three general overall categories of response are proposed: complete response, partial response, and other. Although the group recognizes the complete and partial responses as the categories of greatest interest, other summary outcomes such as stable disease or mixed response can be also included in clinical trials. Complete overall response is defined as resolution of all reversible manifestations in each organ or site, and partial overall response is defined as improvement in a measure for at least one organ or site without progression in measures for any other organ or site. We do not propose the routine use of the term “stable disease” because the interpretation depends too heavily on the prior trajectory of the disease, as discussed above.

Global Ratings, Patient-Reported Outcomes, and Performance Measures

The terms “complete response,” “partial response,” and “progression” do not technically apply to subjective or functional measures data. Instead, the definition of improvement or worsening for such scales is based on the reliability of the measure (the variability caused by measurement error) and is anchored against clinically perceptible changes. For global ratings and categorical scales, a 1-point change on a 3- or 7-point scale or a 2- to 3-point change (0.5 SD change) on a 0- to 10-point scale could be considered clinically meaningful, pending further evaluation in the chronic GVHD population. Unless otherwise specified, for all patient-reported measures, a change of 0.5 SD may be considered clinically meaningful [64,65]. A distribution-based analysis was used to define improvement as a change of 6 to 7 points (0.5 SD) on the chronic GVHD symptom summary scale [12].

Impairments of grip strength, walk time, and range of motion are measured by comparison with normative values. Minimal clinically meaningful improvements for these measures are provisionally defined as a 25% decrease in the level of impairment as compared with baseline. For HAP, clinically meaningful improvement is defined as a 10-point increase in the maximum activity score, because a change of this magnitude is sufficient to change the disability category at the middle of the scale.

USE OF RESPONSE ASSESSMENT AS A PRIMARY END POINT IN CLINICAL TRIALS

Beyond providing tools for assessment of response, clinical protocols must select appropriate primary and secondary end points. A primary end point represents the principal basis by which the success or failure of a treatment will be decided, whereas secondary end points are selected to be supportive of the primary end point or to demonstrate that the benefit provided with respect to the primary end point is not offset by a detrimental effect on other disease manifestations. Prespecified expectations regarding effects of a study intervention on the primary end point also provide the basis for statistical power calculations used to determine the number of patients to be enrolled. If a trial is going to be used for the marketing approval of therapy, regulatory authorities should be included early in the planning.

Table 4 summarizes the potential use of organ measures as primary end points in chronic GVHD clinical trials. Any of the listed assessments could be used as a secondary end point, with or without blinding, but the validity of subjective assessments in open-label trials will always be open to question. The list of assessments in this table is limited to measurements and scales that could be used by a general internist or pediatrician or by patients. More sophisticated assessments of certain organs such as skin, eyes, mouth, female genital tract, and joints may be needed for certain studies [30-40]. Specialized expertise will be needed for these assessments, and the criteria for measurement of response in these situations exceed the scope of the current proposal.

Some of the response scales in Table 4 measure clinical benefit, whereas others measure potential clinical benefit as reflected by a surrogate end point. For example, in cardiovascular disease, well-established surrogate end points such as blood pressure or serum cholesterol can be used for regulatory approval. Less well-established surrogate end points could be used in certain circumstances if they are reasonably likely to predict clinical benefit. Elevated serum bilirubin levels at the onset of chronic GVHD have been associated with an increased risk of nonrelapse mortality [1], but validation studies have not been carried out to show that improvement in serum bilirubin levels is associated with prolonged survival among patients with chronic GVHD. Evaluation of other liver function tests in patients with chronic GVHD has also not been reported. For this reason, the acceptability of improved liver function tests as a basis for approval remains uncertain at this time.

Some of the response scales in Table 4 involve objective assessments, whereas others involve subjective assessments. Blinding of treatment arms to prevent bias is recommended whenever feasible, espe-

Table 4. Potential Use of Chronic GVHD-specific Measures as Primary End Points in Clinical Trials

Organ and Assessment	Clinical Benefit	Blinding Required
Skin		
Objective assessment	Yes	No*
Pruritus	Yes	Yes
Eyes		
Schirmer's tear test	Yes	No
Ocular discomfort	Yes	Yes
Mouth		
Objective assessment	Yes	No*
Oral pain	Yes	Yes
Oral dryness	Yes	Yes
Oral sensitivity	Yes	Yes
Hematology	Unknown	No
Gastrointestinal symptoms	Yes	Yes
Liver		
Bilirubin	Unknown	No
Alkaline phosphatase	Unknown	No
Aminotransferase levels	Unknown	No
Lungs	Yes	No
Symptom scale	Yes	Yes
Global rating scales	Yes	Yes
Range of motion	Yes	No*

GVHD indicates graft-versus-host disease.

This table is limited to consideration of possible primary end points.

Any of the listed assessments could be used as a secondary end point, with or without blinding.

*Objective assessments could be enhanced with the use of photographs and/or blinded assessor.

cially when a subjective end point is used as a primary end point in a clinical trial. Even for objective assessments, blinding can be extremely helpful in preventing bias. For example, objective assessments of the skin and mouth can be enhanced through review of serial photographs by a panel of individuals as blinded assessors who have no other information about the patient. A similar approach could also be used in the evaluation of chronic GVHD involving the eye and female genital tract.

FUTURE DIRECTIONS

The proposed response criteria are expected to enhance uniformity of data collection methods and advance standards of chronic GVHD clinical trials but are only provisional and it is imperative that they be tested for reliability and validity in prospective studies. Important tasks for the immediate future include the determination of minimal clinically important changes for some of the measures proposed, determination of most relevant measures, reduction of items, and establishing an outcomes repository for data collected in clinical trials and natural history studies using these instruments. Collaborations with organ-site specialist should be strengthened to develop methods for more sensitive and objective assessment of specific organs. Future studies will be needed to determine the extent to which patient-reported outcomes and functional

measures could be used as a primary end point in chronic GVHD clinical trials. Improved methods will be needed to distinguish chronic GVHD disease activity from irreversible damage and to develop a chronic GVHD activity index for clinical trials, perhaps through the use of biomarkers [66].

NATIONAL INSTITUTES OF HEALTH CONSENSUS DEVELOPMENT PROJECT ON CRITERIA FOR CLINICAL TRIALS IN CHRONIC GVHD STEERING COMMITTEE

Steven Pavletic and Georgia Vogelsang (Project Chairs), LeeAnn Jensen (Planning Committee Chair), Lisa Filipovich (Diagnosis and Staging), Howard Shulman (Histopathology), Kirk Schultz (Biomarkers), Dan Couriel (Ancillary and Supportive Care), Stephanie Lee (Design of Clinical Trials), and James Ferrara, Mary Flowers, Jean Henslee-Downey, Paul Martin, Barbara Mittleman, Shiv Prasad, Donna Przepiorka, Douglas Rizzo, Daniel Weisdorf, and Roy Wu (Members). The project group also recognizes contributions of numerous colleagues in the field of blood and marrow transplantation, medical specialists and consultants, pharmaceutical industry, and the National Institutes of Health and US Food and Drug Administration professional staff for their intellectual input, dedication, and enthusiasm on the road toward completion of these documents.

DISCLAIMER

The opinions expressed here are those of the authors and do not represent the official position of the National Institutes of Health, Food and Drug Administration, or the US Government.

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LIST OF APPENDICES AND ATTACHMENTS AVAILABLE ON THE AMERICAN SOCIETY FOR BLOOD AND MARROW TRANSPLANTATION WORLD WIDE WEB SITE: <http://www.asbmt.org/GvHDForms>

Response Criteria Appendix A: Data Collection Form A—Clinician Assessment

Response Criteria Appendix B: Data Collection Form B—Patient Self-Report

Response Criteria Appendix C: Proposed Calculations for Partial Response in Chronic GVHD

Response Criteria Appendix D: Proposed Calculations for Progression in Chronic GVHD

Response Criteria Attachment 1: Literature Review of Various Response Criteria Used in Chronic Graft-versus-Host Disease Clinical Trials (By Gorgun Akpek)

Response Criteria Attachment 2: Glossary

Response Criteria Attachment 3: Skin BSA Calculation Worksheet

Response Criteria Attachment 4: BSA Assessment in Children Younger than 1 Year of Age

Response Criteria Attachment 5: Patient-Reported Outcome Measures Recommended for Chronic GVHD Response Evaluations

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Editorial

The Future of Chronic Graft-Versus-Host Disease: Introduction to the 2020 National Institutes of Health Consensus Development Project Reports



Steven Z. Pavletic^{1,*}, Paul J. Martin^{2,3}, Kirk R. Schultz⁴, Stephanie J. Lee^{2,3}

¹ Immune Deficiency Cellular Therapy Program, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

² Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington

³ Medical Oncology, University of Washington, Seattle, Washington

⁴ Pediatric Hematology, Oncology, & Bone Marrow Transplant, BC Children's Hospital, Vancouver, BC, Canada

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Chronic graft-versus-host disease (GVHD) remains the most significant long-term complication after successful allogeneic hematopoietic cell transplantation (HCT) affecting 30% to 70% patients [1–3]. Steady improvements in donor availability and survival after allogeneic HCT have increased the number of patients at risk of developing chronic GVHD. Although the population prevalence is low (~15,000 cases in the United States), chronic GVHD represents a continuing challenge due to its complexity and chronicity and the multiplicity of organ-specific medical complications. About 90% of chronic GVHD medical care occurs in the outpatient setting, often in primary oncology–hematology community practices that have limited access to expert subspecialty care. The socioeconomic and financial burdens to patients and the healthcare system are enormous, with total costs including hospitalizations, outpatient visits, and systemic medications to treat chronic GVHD totaling an average of US\$300,000 per patient each year [1].

Unfavorable trends in the incidence and severity of chronic GVHD led to the first National Institutes of Health (NIH) Consensus Development Project on Criteria for Clinical Trials in Chronic GVHD in 2005. The primary goals of this effort were to establish expert recommendations for a common terminology and best practices in clinical trials and biomarker studies toward development of new therapies. The six working group reports have ranked among the most highly referenced publications in the field [4]. In 2014, the second NIH consensus conference was based on a decade of new evidence that further

refined consensus recommendations. This effort helped to define a regulatory pathway leading to the first approval of a drug for treatment of chronic GVHD in the United States [5,6]. The primary endpoint in that trial was clinical overall response based on NIH criteria [6].

The field has now begun to develop novel targeted agents for treatment of chronic GVHD [7]. The scope of the disease and its clinical course are now much more thoroughly characterized, and its complex pathophysiology is better understood than in 2005 [8]. We have an increasing number of investigational agents available for treatment, and resources are now available thanks to greater industry and government funding. This momentum has also led to development of the first US-based National Comprehensive Cancer Network guideline for GVHD management [9]. Although the survival of patients with the most severe forms of chronic GVHD has likely improved due to better supportive care, the algorithm for the selection of appropriate systemic therapy has not changed since the 1980s. Initial treatment still relies on prednisone with or without a calcineurin inhibitor, which does not control the disease in most patients, and trial and error for subsequent treatment. We have no guide for patient-tailored approaches for prevention or pre-emption, and highly morbid disabling forms of chronic GVHD still occur all too frequently. Our goal to eliminate chronic GVHD as a source of patient suffering while improving long-term outcomes after allogeneic HCT remains elusive, although we now have the tools to achieve these objectives.

To address these challenges in a rapidly changing field, a third NIH Consensus Development Project on Criteria for Clinical Trials in Chronic GVHD was initiated in November 2019 after receiving funding from the National Cancer Institute Center for Cancer Research. In contrast to the 2005 and 2014 NIH consensus conferences, the main goal of this project was not to

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*Correspondence and reprint requests: Steven Z. Pavletic, Immune Deficiency Cellular Therapy Program, Center for Cancer Research, National Cancer Institute, National Institutes of Health, 10 Center Drive, Room CRC 4-3130, Bethesda, MD 20892-1907.

E-mail address: pavletis@mail.nih.gov (S.Z. Pavletic).


Chronic GVHD Four Working Groups – 2020 NIH Consensus Framework			
			
Intervention based on pre-transplant characteristics	Intervention based on post-transplant information	Established chronic GVHD per NIH criteria	Severe, advanced chronic GVHD
WG1	WG2	WG3	WG4
Etiology/Prevention	Diagnosis/Preemptive therapy	Systemic treatment	Highly morbid manifestations
Understanding of biologic processes/ Interventions applied based on chronic GVHD risk known before transplant, regardless of when the intervention is given	Early diagnosis/ Interventions applied after transplant based on a higher than previously appreciated risk of developing chronic GVHD based on secondary events, signs, symptoms, or biomarkers	Systemic treatments for established chronic GVHD, including initial and subsequent therapies	Understanding of the biologic differences in highly morbid chronic GVHD manifestations/ local and systemic interventions specifically targeting these morbid conditions

Figure 1. 2020 NIH Consensus Development Project on Criteria for Clinical Trials in Chronic GVHD working groups and their scopes.

standardize or revise clinical research tools but rather to stimulate the field by identifying basic and clinical research directions that may lead to fundamental change in chronic GVHD management over the next 3 to 7 years. The four working groups were charged to “think outside the box,” reexamine accomplishments to date, identify gaps in the field of chronic GVHD and allogeneic HCT, and define the next steps that should be taken to advance the field in a fundamentally new way (Figure 1). Five preliminary manuscripts were written between November 2019 and November 2020. Due to the COVID-19 pandemic, the third NIH Chronic GVHD Consensus Conference was held as a virtual meeting over 3 days through six 2-hour sessions from November 18 to 20, 2020, with 850 registered participants. Based on additional comments from independent external peer reviewers and conference participants and from a 30-day post-conference public comment period, the five reports were further revised for submission to *Transplantation and Cellular Therapy* beginning in February 2021.

Working group 1 was tasked with addressing gaps in knowledge about the donor and recipient etiologic processes that occur early after HCT to incite chronic GVHD. Working group 1 has also introduced the concept of “second hits,” such as viral infections and acute GVHD, that may further incite the pathogenesis of chronic GVHD. “Prevention” is strictly defined as an intervention applied based on chronic GVHD risk information known before transplant, regardless of when the intervention is given. Well-established prevention strategies such as T cell depletion or post-transplant high-dose cyclophosphamide are being tested. The main downside of prevention is that the intervention is given to all subjects regardless of whether or not they are destined to develop chronic GVHD. Accordingly, we have a major unmet need to develop accurate risk-stratification systems to be utilized before or at the time of HCT that would allow personalized approaches for assigning specific chronic GVHD preventive interventions for individual patients.

Working group 2 (two documents) was tasked with proposing strategies for the development of preemptive

approaches to chronic GVHD. “Preemption” is defined as an intervention applied after HCT prompted by secondary events, signs, symptoms, or biomarkers indicating that the risk of chronic GVHD in a patient is higher than had been previously appreciated. Preemptive treatment may be the optimal approach because people who have a high risk of chronic GVHD are treated early, before the onset of manifest disease. Clinical trials are needed to determine whether such early intervention would lower the incidence of moderate to severe chronic GVHD and improve long-term outcomes. Early signs and symptoms of chronic GVHD that are reliably associated with later progression to highly morbid forms of chronic GVHD must be identified. Earlier clinical recognition of chronic GVHD will require greater involvement of non-transplant providers, as well as patients and caregivers, and could be facilitated by technology such as telehealth, teleconferences, and electronic reporting tools.

Working group 3 was tasked with recommending ways to improve systemic treatment for chronic GVHD. Development of effective regimens that reduce or eliminate the need for concurrent corticosteroid treatment is a high priority that was endorsed by patient advocacy groups. Even with best modern therapies for steroid-refractory chronic GVHD, complete response rates are typically <10%, and the disease eventually recurs or progresses in 50% to 70% of patients. The field should move from the current empirical trial-and-error approach to treatment after failure of corticosteroids toward biology-based prognostic algorithms that guide a personalized treatment approach based on selection of specific agents according to clinical and biological profile assessments for each patient. Ultimately, it might be possible to develop adaptive platform protocols that enable rapid clinical screening of new agents in early-phase studies, although new organizational structures will be needed to conduct such trials and simultaneously manage the interests of multiple stakeholders [10].

Working group 4 reviewed highly morbid forms of chronic GVHD, such as lung, skin sclerosis, intestinal tract, and eye

involvement, that pose special challenges due to their disabling and recalcitrant nature. Such patients carry the greatest burden of chronic GVHD symptoms, functional disability, psychosocial dysfunction, and impairments in quality of life. Better understanding of fibrosis in chronic GVHD biology has identified several promising novel targets and combination approaches to be tested. High priorities include the establishment of primary endpoints appropriate for each highly morbid manifestation and the need for novel trial designs that can be informative after enrolling small numbers of patients.

All of the working groups identified development of qualified biomarkers for clinical use as an overarching prominent unmet need. Adhering to standard terminology and guidelines for clinical development and verification of top candidates is imperative. Although a number of potential candidate biomarkers in chronic GVHD have been identified, their clinical development has lagged behind similar efforts in acute GVHD for a variety of reasons, including complex clinical presentation, long time trajectory, and lack of standardization in clinical studies and sample processing. Definitions from the Food and Drug Administration's Biomarkers, Endpoints, and other Tools (BEST) Resource, and the prior NIH conference guidelines should be used to integrate biomarkers into chronic GVHD drug development [11,12].

Unlike prior NIH consensus conferences, the 2020 Consensus Conference included industry and advocacy summits to establish an agenda and foundation for long-term sustainable collaborative efforts of all stakeholders. The industry summit defined the need for tighter collaboration among industry sponsors for trials of combination therapies and proposed the creation of new structures such as research biobanks to compile and facilitate access to samples and data from multi-center trials. The patient advocacy summit identified the need for national and regional networks of centers of chronic GVHD excellence as the highest priority to break barriers in accessing subspecialty care both by patients and their primary providers [13]. Formation of the newly planned Advocacy Consortium was motivated by the often-unrecognized heavy toll that chronic GVHD takes on the long-term well-being of patients, which includes fatigue, depression, cognitive impairment, and overall insufficient resources for support in communities.

Several long-term initiatives and subsequent publications will follow the 2020 NIH Consensus Development Project on Criteria for Clinical Trials in Chronic GVHD. A long-term effort is focused on continuing education and implementation of best practices for chronic GVHD providers through the newly established American Society for Transplantation and Cellular Therapy–NIH–European Society for Blood and Marrow Transplantation chronic GVHD joint education committee. This group is also reaching out to other major professional societies in the fields of hematology and oncology. The 2020 NIH chronic GVHD Consensus international initiative will start addressing global issues related to access to chronic GVHD care and therapy worldwide. Task forces have been formed to produce publication updates focused on priorities in chronic GVHD biology research, chronic GVHD manifestations not covered by the NIH diagnostic criteria and updates on recommendations for clinical trial design.

From its beginning in 2004, the NIH Chronic GVHD Consensus Development Project has prioritized the engagement of a new generation of investigators to enter the field of allogeneic HCT and who have emerged as prominent leaders. This priority will be evident from the authorships and leads of the five papers scheduled for publication in *Transplantation and Cellular Therapy* starting with the current issue [14]. All 2020 NIH Chronic GVHD Consensus Development Project documents end with a section

outlining proposed research priorities for the next 3 years and the following 3 to 7 years. We are convinced that the momentum generated during the past decade and a half has brought unprecedented progress in the field of chronic GVHD, addressing a major impediment to full recovery after allogeneic HCT. Our goal is that by the time we hold the fourth NIH Consensus Development Project on Criteria for Clinical Trials in Chronic GVHD conference, most of the unknowns will become knowns, and the prevention and treatment of chronic GVHD will have improved substantially for the benefit of our patients and all concerned.

DECLARATION OF COMPETING INTEREST

S.Z.P. has no conflicts of interest to report. P.J.M. is has served on advisory boards for Mesoblast and Rigel Pharmaceuticals, Inc., and has received honoraria from Janssen. K.R.S. is a data and safety monitoring board member of Bristol Myers Squibb/Juno and is on the advisory boards of Jazz, Novartis, and Janssen. S.J.L. has received research funding from Amgen, AstraZeneca, Incyte, Novartis, Pfizer, Syndax, and Takeda and is on the steering committee of Incyte.

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APPENDIX: STEERING COMMITTEE OF THE 2020 NIH CONSENSUS DEVELOPMENT PROJECT ON CRITERIA FOR CLINICAL TRIALS IN CHRONIC GVHD

Chairs: Steven Pavletic, MD, MS, National Cancer Institute; Stephanie J. Lee, MD, MPH, Fred Hutchinson Cancer Research Center; Kirk Schultz, MD, University of British Columbia; Daniel Wolff, MD, University of Regensburg

Members: Hildegard Greinix, MD, University of Graz; Sophie Paczesny, MD, University of South Carolina; Bruce Blazar, MD, University of Minnesota; Stefanie Sarantopoulos, MD, PhD, Duke University; Joseph Pidala, MD, PhD, Moffitt Cancer Center; Corey Cutler, MD, MPH, FRCPC, Dana Farber Cancer Institute; Gerard Socie, MD, PhD, St-Louis Hospital, Paris; Paul J. Martin, MD, Fred Hutchinson Cancer Research Center; Meredith Cowden, MA, LPCC-S, Cowden Foundation; Linda Griffith, MD, National Institute of Allergy and Infectious Diseases (ex officio)

Lead editors: Paul J. Martin, MD, Fred Hutchinson Cancer Research Center (working groups 1 and 3); Stephanie J. Lee, MD, MPH, Fred Hutchinson Cancer Research Center (working groups 2 and 4).

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7. ABSTRACT

Allogeneic hematopoietic stem cells in peripheral blood transplantation (alloPBSCT) or bone marrow transplantation (alloBMT) have different biological characteristics which may affect differently prognostic factors for incidence and severity of chronic graft-versus-host disease (cGVHD). The first study included 87 patients who survived at least 100 days after matched related donor myeloablative transplantation. Factors significantly associated with higher incidence of cGVHD after alloPBSCT included CMV-positive donor, acute skin GVHD, and diagnoses other than lymphoma. The data suggest there some cGVHD prognostic factors are unique to recipients of alloPBSCT

The second study was based on the donor-derived T cells, by analyzing their impact of *ex vivo* on cGVHD was analyzed in a randomized multicenter trial involving unrelated donor marrow transplants. A total of 404 patients diagnosed with hematologic malignancies received a total body irradiation–based myeloablative conditioning regimen. Survival at 3 years from diagnosis of cGVHD was similar, in the same way as the proportion of patients with cGVHD who discontinued immunosuppression. Incidence of serious infections and leukemia relapse were similar on both treatment arms. In spite of a significant reduction of acute GVHD, TCD did not reduce the incidence of cGVHD or improve survival in patients who developed it. Lastly, the National Institutes of Health (NIH) Chronic Graft-versus-Host Disease (GVHD) Consensus Response Criteria Working Group recommended several measures to document serial evaluations of chronic GVHD organ involvement. Provisional definitions of complete response, partial response, and progression were proposed for each organ and for the overall outcome. Based on publications over the last 9 years, the 2014 Working Group has updated its recommendations for measures and interpretation of organ and overall responses.

Major changes include eliminating several clinical parameters from the determination of response, updating or adding new organ scales to assess response, and recognising that progression excludes minimal, clinically insignificant worsening that does not usually warrant a change in therapy. The response definitions have been revised to reflect these changes and are expected to enhance these measures' reliability and practical utility in clinical trials. Clarification is provided about response assessment after the addition of topical or organ-targeted treatment. Ancillary measures are strongly encouraged in clinical trials. Areas suggested for additional research include criteria to identify irreversible organ damage and validation of the modified response criteria, including in the pediatric population. A synergy of these papers provides an overview of the approaches to handling CGVHD disease in an evidence-based manner.

8. SAŽETAK

Alogene hematopoetske matične stanice u transplantaciji periferne krvi (alloPBSCT) ili transplantaciji koštane srži (alloBMT) imaju različite biološke karakteristike koje mogu utjecati na prognostičke čimbenike za incidenciju i opseg reakcije presatka protiv domaćina (cGVHD). Prva studija uključila je 87 pacijenata koji su preživjeli najmanje 100 dana nakon mijeloablativne transplantacije srodnog donora. Čimbenici koji su značajno povezani s većom učestalošću cGVHD-a nakon aloPBSCT-a uključivali su CMV-pozitivnog davatelja, akutni kožni GVHD i druge dijagnoze osim limfoma. Podaci sugeriraju da su neki cGVHD prognostički čimbenici jedinstveni za primatelje aloPBSCT-a.

Druga studija temeljila se na T stanicama dobivenim od donora, analizom njihovog utjecaja ex vivo na cGVHD u multicentričnom ispitivanju koje je uključivalo transplantacije srži nesrodnih donora. Ukupno 404 pacijenata s dijagnozom hematoloških zloćudnih bolesti primilo je režim mijeloablativnog kondicioniranja temeljen na zračenju cijelog tijela. Preživljenje nakon 3 godine bilo je slično, na isti način kao i udio pacijenata s cGVHD-om koji su prekinuli imunosupresiju. Učestalost ozbiljnih infekcija i recidiva leukemije bili su slični u obje skupine liječenja. Unatoč značajnom smanjenju akutnog GVHD-a, TCD nije smanjio incidenciju cGVHD-a niti poboljšao preživljenje pacijenata koji su se razvili. Naposljetku, radna skupina za kriterije odgovora Nacionalnog instituta za zdravlje (NIH) za kroničnu bolest transplantata protiv domaćina (GVHD) preporučila je nekoliko mjera za dokumentiranje serijskih procjena kronične zahvaćenosti GVHD organa. Za svaki organ i za ukupni ishod predložene su privremene definicije potpunog odgovora, djelomičnog odgovora i progresije. Na temelju publikacija u posljednjih 9 godina, radna skupina iz 2014. ažurirala je svoje preporuke za mjere i tumačenje odgovora organa i ukupnih odgovora.

Glavne promjene uključuju eliminaciju nekoliko kliničkih parametara iz određivanja odgovora, ažuriranje ili dodavanje novih ljestvica organa za procjenu odgovora i prepoznavanje da progresija isključuje minimalno, klinički beznačajno pogoršanje koje obično ne opravdava promjenu terapije. Definicije odgovora su revidirane kako bi odražavale te promjene i očekuje se da će povećati pouzdanost i praktičnu korisnost ovih mjera u kliničkim ispitivanjima. Dano je pojašnjenje o procjeni odgovora nakon dodavanja lokalnog liječenja ili liječenja usmjerenog na organe. Pomoćne mjere snažno se potiču u kliničkim ispitivanjima. Područja predložena za

dodatna istraživanja uključuju kriterije za prepoznavanje ireverzibilnog oštećenja organa i validaciju modificiranih kriterija odgovora, uključujući i pedijatrijsku populaciju. Sinergija ovih radova daje pregled pristupa liječenju CGVHD bolesti, na način utemeljen na dokazima.

CURRICULUM VITAE

Name: Steven Z. Pavletic, M.D., M.S.

Citizenship: United States

Current Position:

Head, GVHD and Late Effects Section, Immune Deficiency Cellular Therapy Program
Senior Clinician, NIH Multidisciplinary Clinic, Chronic GVHD Study Group,
Clinical Director NCI Myeloid Malignancy Program
Center for Cancer Research, National Cancer Institute, National Institutes of Health
Bethesda, Maryland, 10 Center Drive, Building 10, Room CRC 4-3130
Phone: 301-402-4899, 301-204-9702, Email: pavletis@mail.nih.gov

Area of Clinical and Research Interests:

Allogeneic transplantation for hematologic malignancies, Graft versus Host Disease and Graft -versus Leukemia/Lymphoma Effects, CAR T-cell therapy, Complications of cellular and immunotherapy

Brief Chronology of Employment:

2020 – present	Clinical Director, NCI Myeloid Malignancy Program, NCI, CCR, NIH
2015-present	Senior Clinician, Center for Cancer Research, National Cancer Institute, NIH, Bethesda, Maryland. Head, Graft-versus-Host and Late Effects Section, National Cancer Institute, Bethesda, Maryland
2012-present	Adjunct Professor of Medicine and Oncology, Georgetown University, Lombardi Cancer Center, Washington DC
2002-2015	Head, Graft-versus-Host and Autoimmunity Unit, National Cancer Institute, Experimental Transplantation and Immunology Branch, Bethesda, Maryland
2005-2007	Acting Chief, Medical Oncology Transplantation and Immunotherapy Service, NCI
2002-present	Adjunct appointment at the National Institute for Arthritis and Musculoskeletal and Skin Diseases
2007-present	Adjunct appointment at the Medical Oncology Service, National Cancer Institute, NIH
2004-present	Visiting Professor, University of Zagreb School of Medicine, Zagreb, Croatia
2000-2002	Associate Professor of Medicine, Section of Oncology/Hematology, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska
1999-2002	Director, Allogeneic Stem Cell Transplantation, University of Nebraska Medical Center, Omaha, Nebraska
1997-2000	Assistant Professor of Medicine, Section of Oncology/Hematology, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska
2000-2002	Fellow, Graduate Faculty, University of Nebraska Medical Center, Omaha, Nebraska

1997-2002	Member, Eppley Cancer Center, University of Nebraska Medical Center, Omaha, Nebraska
1989-1990	Staff Physician and Instructor in Medicine, Department of Internal Medicine, Division of Hematology, Rebro University Hospital and University Medical School, Zagreb, Croatia
1980-1988	Clinical Hospital Center and University Hospitals, Zagreb, Croatia, research associate and postgraduate training
1979	Institute for Automobile Traffic Medicine, internship

Education:

1979	M.D., Zagreb University School of Medicine Zagreb, Croatia
1980	Clinical Intern, Rebro University Hospital, Zagreb, Croatia
1983	M.S. (Immunology) Zagreb University School of Medicine, Zagreb, Croatia
1989	Internal Medicine Resident and Hematology Postgraduate Training, Rebro University Hospital, Zagreb, Croatia
1992	Bone Marrow Transplant Fellow, Clinical Research Division, Fred Hutchinson Cancer Research Center and University of Washington Medical School, Oncology Division, Seattle, Washington
1995	Internal Medicine Resident, University of Nebraska Medical Center, Omaha, Nebraska
1997	Oncology/Hematology Fellow, University of Nebraska Medical Center, Omaha, Nebraska

Medical License and Board Certifications

Active	Medical License, State of Nebraska, #19167
Inactive	Temporary Educational Permit, State of Washington, #252-14, File #003521
Inactive	Medical License, Republic of Croatia, #06-5748
1999	Diplomate, American Board of Internal Medicine, Hematology, #160613
1995	Diplomate, American Board of Internal Medicine, #160613
1999	Diplomate, American Board of Internal Medicine, Oncology #160613
1992	FLEX, #560125025
1992	ECFMG, #9625D

Societies:

2018-present	Croatian Academy of Sciences and Arts, Corresponding Member
1995-present	American Society for Blood and Marrow Transplantation (ASTCT now)
1994-present	Alpha-Omega-Alpha Honor Medical Society
1993-present	American Society for Hematology
1993-2003	American Society for Clinical Oncology
2011-2015	Central Eastern European Leukemia Group
1997-2002	The Myelodysplastic Syndromes Foundation
1998-2002	American Federation for Medical Research
1997-2002	Nebraska Leukemia Network
1997-2002	Nebraska Lymphoma Study Group
1997-2002	CALGB

1993-2000	2002 Omaha Medical Society
1993-2000	2002 Nebraska Medical Society
1993-2003	American College of Physicians (Fellow 2001)
1992-2002	2002 American Medical Association
1992-2002	2002 American Association for Cancer Research
1990-1994	The Seattle Blood Club
1988-2002	International Society for Experimental Hematology
1979-1990	Croatian Medical Association

Editorial Boards:

2009	Textbook Chief Editor, with Vogelsang G. Chronic GVHD: Principles and Practice of Interdisciplinary Management. 1 st Edition, Cambridge University Press, New York.
2006-present	Editorial Board Member, <i>Bone Marrow Transplantation</i>
2005-present	Editorial Board Member, <i>Biology of Blood and Marrow Transplantation</i> (Journal of the American Society for Blood and Marrow Transplantation, JTCT now)
2001	Guest Editor, “The Current Role of Hematopoietic Stem Cell Transplantation in Rheumatoid Arthritis”, <i>Journal of Rheumatology</i> , Supplement 64, vol. 28
1992-1997	Advisory Board, <i>Libri Oncologici</i> (Journal of Croatian Cancer Society)
1976-1979	Editorial Board, <i>Medicinar</i> , Zagreb University School of Medicine, Zagreb, Croatia.
1989	Guest Editor, <i>Bone Marrow Transplantation</i> , vol. 4. Supplement 3

Ad hoc reviewer for many leading journals in the field of hematology-oncology and hematopoietic cell transplantation or high end medical journals.

Committees and Boards:

2021-present	ASH subcommittee for immunotherapies, member
2021-present	ASH subcommittee for precision medicine, member
2018-present	ASTCT paper writing committee on standardized CAR-T toxicities grading (ASH representative)
2019- present	CIDR stakeholders council on cellular immunotherapy (ASH representative)
2021	ASH abstracts reviewer
2020-present	ASH Workshop on CAR T biomarkers development co-chair
2018-2021	CIBMTR nominating committee full member
2019-2022	CIBMTR advisory committee member
2020-present	European School of Oncology 40 th anniversary book writing committee – Contributions of European Oncology
2017-present	Full member of the NCI CCR intramural scientific review committee
2021-present	NCI CCR PEIP search committee
2017	NCI CCR Senior Clinicians search committee
2017-present	Co-director, NCI-NHLBI Fellowship Hematologic Malignancies - Immunotherapy and Transplant Journal Club Conferences
2016-2020	American Society of Hematology Immunotherapy Task Force- first co-chair with Dr. Sophie Paczesny (chief organizer, July 2018 1 st ASH Summit, Washington DC)

2016-present Data Safety Monitoring Committee - Lombardi Cancer Center Georgetown University, Washington DC

2015-2020 American Society of Hematology Precision Medicine Task Force-member

2015-present NIH/HRSA Consensus Project on late effects after transplantation, Steering committee member

2015-2018 CIBMTR Advisory Committee Member at large

2017 American Society of Hematology annual meeting abstract reviewer committee review section chair

2016 American Society of Hematology annual meeting abstract reviewer and the GVHD session chair

2004-present 2004, 2014 and 2020 NIH Consensus project on criteria for clinical trials in Chronic GVHD co-chair.

2003-present Chair, NIH Chronic GVHD Study Group

2021 CTN SOSS, GVHD WG

2014 CTN SOSS, autoimmune disease and GVHD WG

2011-2015 ASH Transplant immunology committee member, (2014 co-chair, 2015 chair and meeting chair)

2012-2020 Georgetown University-Ana Rukavina Foundation joint fellowship in hematologic malignancies-advisory committee member

2012-2020 Co-Chair, NCI Center for Global Health, European Regional Interest Group

2012 ASBMT CIBMTR Tandem Meetings Plenary Session Chair-Transplantation for Autoimmune Disease

2011-2013 Lupus Society of America, research grant reviewer

2011 Grant Reviewer-UK EME Programme

2010-present European Blood and Marrow Transplant Group (EBMT) annual meeting abstract reviewer

2010-present DSMB- Fred Hutchinson Cancer Research Center-allotransplantation for SScl and for Crohn's dis.

2010-2011 DSMB-NHLBI, alternate member

2010-2018 Georgetown University Hospital and Lombardi Cancer Center/NCI Joint BMT Initiative

2010 NCI sponsored national chronic lymphocytic leukemia advisory board, co-chair "High risk CLL and transplantation subcommittee", Rockville, Maryland.

02/2010 ASBMT-CIBMTR Tandem Meetings, Orlando, Florida, Chair: "Bronchiolitis Obliterans Syndrome after allogeneic hematopoietic cell transplantation"

2008 and 2012 Reviewer-NIH, Warren G. Magnuson Clinical Center, Department of Rehabilitation Medicine Operational Review

2008 FDA CDER ad hoc protocol consultant

June 19-20, 2008 Planning Committee member and introductory talk: NCI Workshop-Lung Cancer in Croatia, Zagreb.

07/2007 Co-Chair, US-Croatian Oncology Task Force.

May 11-14 2007 Co-Chair-High level NIH-NCI-EU-Croatian Workshop-Strategies for the development of clinical oncology in Croatia-a model of a transitioning country", Zagreb, Croatia

2007- present Croatian Ministry of Science, ad hoc grant reviews

2004- present NIH Consensus project on criteria for clinical trials in chronic GVHD, co-chair

2004 CIBMTR GVHD committee (chair 2004-2010)

2004 CIBMTR Autoimmune Disease committee (chair 2010-2014)

2004-present	CIBMTR Chronic Leukemia Committee
2002-present	Blood and Marrow Transplant Clinical Trials Network Steering Committee (ex officio seat)
2004-present	HRSA inter agency group committee member
2004	Dutch Arthritis Association-grant reviewer
2003-2004	DSMB, a multi-center trial of acute GVHD prevention using a novel method of cell selection, PI Dennis Confer, National Marrow Donor Program, Minneapolis, Minnesota
2002	Member, Internal Medicine Chairman's Research Council, University of Nebraska Medical Center, Omaha, Nebraska
2001-2002	Member, University of Nebraska Medical Center/Nebraska Health Systems Institutional Review Board
2002	Reviewer, ASH 2002 educational session textbook
1997	Chronic Leukemia Committee, International Bone Marrow Transplantation Registry
1997-2003	Autoimmune Disease Committee-RA Working Group, International Bone Marrow Transplantation Registry
2001 and 2002	Grant reviewer, NMDP, Amy Strelzer Manasevit Research Program
2001	Abstract reviewer. American Society of Hematology annual meeting
2000	Judge, Midwest Student Biomedical Research Forum.
1999	National Marrow Donor Program (institutional director or co-director)
1998-2002	International Project HSCT in CLL member
1998-2002	National Autoimmune Disease Stem Cell Transplantation Collaborative Study member

Principal investigator on Clinical Research and Development Agreements:

CRADA 02328	Closed	06/07/2010	Celgene
CRADA 03050	Closed	2/22/2016	Actelion Pharmaceuticals Ltd
CRADA 03069	Active	8/25/2016	Eli Lilly and Company
CRADA 03273	Active	10/18/2018	Kadmon
CRADA 03211	Active	9/23/2020	Pharmacyclics
CRADA 03360	Active	12/9/2020	CTI Biopharma
CRADA pending	N/A	2021	BMS

Selection of Invited Talks (not tracking since 2018 available upon request):

June 29, 2018	George Washington University Cancer Center Consortium, Washington DC - What's new in cGVHD?
May 30, 2018	Vanderbilt University, cGVHD What comes next?
May 14, 2018	Stanford University, New treatments in cGVHD
March 14-15, 2018	EBMT Annual meeting, Lisbon, Portugal – 3 invited lectures, cGVHD
February 22, 2018	ASBMT-CIBMTR Tandem, Meet the Professor, chronic GVHD
November 17, 2017	Lung GVHD, Falk Symposium, University of Regensburg, Germany
October 28, 2017	Ocular and systemic cGVHD Symposium, University of Illinois, Chicago
October 21, 2017	GVHD CBMTG Symposium, Montral, Canada
September 22, 2017	Croatian Hematology Society, Plenary Session, New Treatments in cGVHD

June 19, 2017	University of Michigan, Targeted Therapies in cGVHD
October 22, 2016	Ocular and systemic cGVHD Symposium University of Illinois, Chicago
September 24, 2016	9 th Croatian Internal Medicine Conference-Late effects after HSCT
May 1, 2016	ARVO, Seattle, Chronic GVHD Symposium
April 2-5 2016	EBMT Valencia, Chronic GVHD updates
March 2016	University of Miami, Chronic GVHD in 2016
September 2015	Duke University, Updates in chronic GVHD
June 11, 2015	University of Chicago, BMT grand rounds: Chronic GVHD
October 26, 2014	Zagreb, Croatia, EORTC Leukemia Working Party-chronic GVHD-a model for clinical drug development
October 24, 2014	Warsaw, speaker, EBMT educational course on late effects after transplantation-2014 chronic GVHD consensus
September 2014	20th Anniversary of the NIH transplant programs Symposium-opening lecture "Unique NIH research environment-chronic GVHD program"
February 2014	HRSA, Bethesda-progress in chronic GVHD
January 2014	University of Pittsburgh Medical Center, visiting professor, "Chronic GVHD"
November 4, 2010	GVHD Conference, Keynote Speaker "Current challenges in diagnosis and management of chronic GVHD", Case Western Reserve University, Cleveland Clinic and Meredith Cowden Foundation, Cleveland, Ohio
October 28, 2010	Georgetown University Hospital Internal Medicine Grand Rounds speaker, "Chronic GVHD-a model to study challenges in cancer survivorship", Washington DC
July 11, 2010	MDS and Aplastic Anemia Society, "Hematopoietic stem cell transplantation for AA and MDS", Annual Survivorship Conference, Bethesda, Maryland
June 17, 2010	Embassy of Croatia, Washington DC, monthly lecture series- "Cancer and US-Croatian collaborations in oncology"
April 27 2010	NIH conference Hairy cell leukemia in second half century, Bethesda, Maryland "Allogeneic transplantation for HCL".
March 27, 2010	Croatian Oncology Society, Cavtat, "Allogeneic transplantation for lymphoma"
March 24, 2010	EBMT Vienna, Workshop lecture "Bronchiolitis Obliterans"
January 2010	Uniformed Services University, Bethesda, Maryland-Immunology PhD/MD PhD Curriculum Lecture "Hematopoietic Stem Cell Transplantation".
December 2012	NMBTLink "The Future of Survivorship" event-invited keynote speaker "Survivorship Challenges-Chronic GVHD".
November 6-7, 2009	University of Regensburg, Germany, "Consensus conference on clinical practice in cGVHD", invited presenter, sessions chair and invited discussant.
June 10, 2009	NHLBI, NIH, BMT Section Seminar- "Diagnosis of cGVHD"
May 8, 2009	NICHD, NIH- "Chronic GVHD" lecture
September, 2008	BMT survivorship-chairperson and presenter, BMT Infonet, Dallas, Texas
July 19 2008	CME course in late effects after hematopoietic stem cell transplantation-2 talks- "Diagnosis of chronic GVHD" and "Practical workshop- challenges in cGVHD management"; Organizer: Fred Hutchinson Cancer Research Center' San Francisco, California.

April 25, 2008 Croatian Oncology Congress, Plenary Lecture: "Late effects after cancer therapy-facing our new challenges".

April 28, 2008 University of Rijeka, Invited lecturer: "Chronic GVHD-an opportunity to advance translational and clinical research. Rijeka, Croatia.

May 1, 2008 European School of Hematology, Course in Bone Marrow Transplantation, lecture on chronic GVHD-Zagreb, Croatia.

April 2, 2008 34th annual EBMT Meeting-Plenary lecture: "New classifications in chronic GVHD", Firenze, Italy.

March 29, 2008 2nd EBMT patients and family day, Plenary lecture, "Progression of GVHD", Firenze, Italy.

October 29, 2007 Mayo clinic transplant center grand rounds, "Chronic GVHD-current trends."

October 3, 2007 1st US-Croatian Conference on ICT-Biotechnology and Pharmaceutical Industry, Split, Croatia, "Addressing Challenges in the new drug development for cancer and chronic illness-model of chronic GVHD".

September 17, 2007 MD Anderson Cancer Center and Zagreb University Leukemia and Lymphoma 2007 conference "Where the East meets West"-Dubrovnik, Croatia, Invited lecture: "Chronic GVHD-new approaches and challenges".

03/2007 Johns Hopkins University, "Hematopoietic stem cell transplantation for autoimmune disease".

2007 ASBMT-CIBMTR Tandem Meetings 2007- "Developing response measures in chronic GVHD", plenary session.

09/2006 NMBMTLink "Advances in bone marrow transplantation", Sunday brunch keynote speaker.

05/2006 "Assessing responses in chronic GVHD" French group for bone marrow transplantation annual meeting, Paris, France.

03/2006 "Allogeneic hematopoietic stem cell transplantation"-Visiting Professor-10 hour of lectures at the University of Zagreb, Croatia.

03/2006 "NIH Response criteria in chronic GVHD", Annual EBMT meeting, Educational Session, Hamburg, Germany.

02/2006 "Chronic GVHD" University of Alabama Birmingham

11/2005 CCR Grand rounds- "Chronic GVHD"

October 17, 2005 "Hematopoietic Stem Cell Transplantation for Autoimmune Disease" DC Rheumatology Society Meeting, Washington DS.

October 5-7, 2005 "Chronic GVHD-Clinical and Scientific Progress" International Symposium on Cellular Therapy for the Treatment of Autoimmune Diseases, Newport Beach, California.

September 21, 2005 NIH Initiatives in Chronic GVHD, 1st International Conference on Pediatric Hematopoietic Stem Cell transplantation and the PBMCT Annual Meeting, Vancouver, British Columbia, Canada.

June 16-17, 2005 Use of non-myeloablative allogeneic stem cell transplantation for autoimmune disease. "Transplantation tolerance-myth or reality"-British Immunology Society Meeting, University of Newcastle, Great Britain.

October 5, 2004 "Hematopoietic stem cell transplantation for SLE", Lupus Research Institute scientific meeting special lecture, New York City.

September 11-14, 2004 Non-myeloablative conditioning regimens for B-cell chronic lymphocytic leukemia. 7th Seminar, New trends in the treatment of acute leukemia. Dubrovnik, Croatia.

September 11-14, 2004 Use of rituximab in B-lymphoproliferative malignancies. 7th Seminar, New trends in the treatment of acute leukemia. Dubrovnik, Croatia.

June 22, 2004 "Transplantation for severe SLE": Lupus Federal Meeting, Bethesda, MD.

February 5-8, 2004 The role of nucleoside analogs as immunosuppressants in hematopoietic stem cell transplantation. 6th International Conference on New Trends in Immunosuppression, Salzburg, Austria, (Invited plenary session lecture).

October 24, 2003 "Non-myeloablative allogeneic stem cell transplantation-an update", 3rd Croatian Congress of Hematology and Transfusion Medicine with International Participation, Opatija, Croatia. (Plenary lecture).

May 28, 2003 "Hematopoietic stem cell transplantation for autoimmune disease", NIAMS regional rheumatology meeting.

May 24, 2003 "ABC of Graft-versus-Host disease", Annual Meeting of American Association of Physician Assistants, New Orleans, LA.

September 12, 2003 "Cytopenias and Myelodysplastic Syndromes", 12th Annual oncology update for primary care physicians, Alegent Health, Omaha, Nebraska.

February 8, 2003 "Nonmyeloablative stem cell transplantation", 20th anniversary of bone marrow transplantation in Zagreb symposia, Zagreb, Croatia.

May 21, 2003 "Pentostatin/rapamycin for the treatment of chronic GVHD". 1st workshop on pathophysiology and new targets in chronic GVHD", Baltimore, MD.

January 19, 2002 "Immunomodulatory effects of pentostatin in a protocol of non-myeloablative stem cell transplantation", 3rd International NST Workshop, Captiva Island, Florida.

March 21, 2002 "Stem Cell Transplantation for autoimmune disease", URN Conference, Scottsdale, Arizona.

September 27, 2002 "Complications of Allogeneic Transplantation", 5th National Annual Meeting of Physicians Assistants in Oncology, Omaha.

December 6, 2002 "Non-myeloablative stem cell transplantation for low-grade lymphoproliferative disease", ASH Super Friday session sponsored by State University of Ohio.

February 11, 2002 "SCT for rheumatoid arthritis" University of Arizona, Tucson.
"Transplantation from Unrelated Donors for Chronic Lymphocytic Leukemia and Lymphoma".

June 14, 2001 National Marrow Donor Program.

December 3, 2001 "Acute GVHD", St Lukes Hospital, Kansas City.

12/2001 "Unrelated Donor Bone Marrow Transplantation for CLL" NMDP Scientific Session, "Super Friday", ASH.

November 10, 2001 "Unrelated Donor Bone Marrow Transplantation for CLL" NMDP Council meeting, Scientific Session, Minneapolis, MI.

October 4-5, 2001 "Hematopoietic Stem Cell Transplantation for Rheumatoid Arthritis", International Symposium: "Hematopoietic Stem Cell Transplantation for Autoimmune Disease", City of Hope National Cancer Center, Duarte, California.

August 29, 2000 "The Role of Hematopoietic Stem Cell Transplantation in the Treatment of B-cell Chronic Lymphocytic Leukemia". Internal Medicine Grand Rounds, University of California at Irvine, Irvine, California.

June 23, 2000 "Transplantation Aspects". Annual European Congress of Rheumatology, Nice, France.

April 6, 2000 “The Role of Hematopoietic Stem Cell Transplantation for Autoimmune Diseases”. National Cancer Institute, Bethesda, Maryland.

April 16, 2000 “The Role of Hematopoietic Stem Cell Transplantation for Autoimmune Diseases”. University of Minnesota, Minneapolis, Minnesota.

August 2, 2000 “The Role of Hematopoietic Stem Cell Transplantation in the Treatment of B-CLL”. Fred Hutchinson Cancer Research Center, University of Washington, Seattle, Washington.

October 9, 2000 “The Role of Hematopoietic Stem Cell Transplantation in the Treatment of Hematological Malignancies”. University of Zagreb.

January 27, 1999 “A New Application: Bone Marrow Transplantation for Autoimmune Disorders”, United Resource Networks Transplant Conference, Naples, Florida.

October 4-5, 1999 “Bone Marrow Transplantation for Autoimmune Diseases”, LifeTrac Network Transplant Conference, Minneapolis, MN.

September 24-25, 1999 “Clinical Experience in the Nebraska Trial for Rheumatoid Arthritis”. University of Massachusetts Medical School Worcester Translational Research Conference, Stem & Immune Cell Therapy for the Treatment of Autoimmune Disease, Worcester, Massachusetts.

October 26, 1999 “The Evolving Role of the Hematopoietic Stem Cell Transplantation for B-CLL”. Transplant and Cellular Therapy Unit-Institut Paoli Calmettes, Marseille, France.

March 19-20, 1998 “New approaches to HSCT” Haploidentical Hematopoietic Stem Cell Transplantation: Current Strategies and Future Directions, Omaha, NE.

January 27, 1998 “Hematopoietic Stem Cell Transplantation for Severe Autoimmune Disease”, United Resource Network, Minneapolis, MN.

November 5, 1997 “Hematopoietic Stem Cell Transplantation for B-CLL”, Creighton University Internal Medicine Grand Rounds.

Chairman and or presenter (not tracking since 2018 available upon request)

July 12-13, 2018 1st ASH summit on immunotherapies for hematologic disease, Task force co-chair, breakout session presenter

March 24, 2017 Chronic GVHD Biomarkers Consortium, Co-chair, Marseille, France

Since 2010 Co-chair, GVHD Symposium, Meredith Cowden Foundation

Since 2009-3/annually opening talk presenter at the NBMtLink patient advocacy group telephone chronic GVHD patient support group

September 20-21, 2016 3rd Symposium and advanced international course in chronic GVHD, Zagreb, Croatia

December 2015 ASH Orlando, Scientific Committee Chair-T cell immunotherapy for hematologic malignancies

September 2015 MDACC leukemia lymphoma, Dubrovnik, Croatia

May 28, 2015 CGVHD and late effects 2nd international symposium, Zagreb, Croatia

November 2013 Regensburg, Germany, cGVHD Symposium

03/2007 Co-Chair-NIH Consensus Conference on chronic GVHD follow up Workshop-Bethesda, Maryland

02/2007 ASBMT/CIBMTR Tandem Meetings, Keystone, Colorado-Plenary Session Chair- “Advances in Chronic GVHD”

06/2006 “Chronic GVHD for medical oncologists”-Chair and presenter, Clinical problems in oncology, ASCO annual meeting, Atlanta, Georgia.

02/2006 Educational workshop: NIH response criteria for chronic GVHD”– chair and presenter, Tandem ASBMT/CIBMTR meetings, Honolulu, Hawaii.

2004- present Co-chair, NIH consensus development project on criteria for clinical trials in chronic GVHD.

02/2005-present Steering committee ex officio member-BMT Clinical Trials Network, also Chronic GVHD Committee member.

2004-present Chair-chronic GVHD response criteria working group, NIH Consensus Project on chronic GVHD

2004- 2010 Co-chair, CIBMTR GVHD Committee

10/2006 Co-Chair-NIAID/NCI Workshop “Considerations in allogeneic stem cell transplantation for non-malignant disease including autoimmune disease”, Bethesda, Maryland

3/2005 Co-Chair-NIAID/NCI Workshop “Feasibility of allogeneic stem cell transplantation for autoimmune disease”, Bethesda, Maryland

12/2004 ASH scientific session co-chair-autologous stem cell transplantation for CLL and autoimmune disease

05/17/2004 Co-Chair 2nd Baltimore-Washington workshop on Chronic GVHD, John Hopkins University, Baltimore, Maryland.

03/2004 Session Chair-ASH 2003 review for Community oncologists in DC area.

May 21, 2003 Co-Chair and Co-Organizer (with G. Vogelsang), 1st Workshop on Pathophysiology and new Therapeutic Targets in Chronic GVHD, Baltimore, Maryland.

02/2003-07/2004 CME course director, “National Cancer Institute Regional Hematological Malignancies Series”, Bethesda, Maryland.

10/25/2002 National CME Course Director: “The Role of Allogeneic Stem Cell Transplantation in the Treatment of Hematologic Malignancies” Omaha, Nebraska.

06/2002 Chairperson, “Stem cell therapy for autoimmune disease”- Rheumatoid arthritis session, Snowbird, Utah.

December 17, 2001 NIH/NIAMS expert panel meeting “Hematopoietic stem cell transplantation in systemic lupus”, Bethesda, Maryland.

12/2001 Session chairman, ASH 2001, “Non-myeloablative regimens and graft-versus tumor effect.”

07/2001-10/2002 NCCN Chronic Myelogenous Leukemia Panel

05/2001 UNMC College of medicine annual seed grant review committee.

01/2001-01/2003 National Marrow Donor Program Research and Publications committee.

03/2000 Chairperson, Special Workshop on the Role of Hematologic Stem Cell Transplantation for Rheumatoid Arthritis, IBMTR/ABMTR Annual Meeting, Anaheim, California.

07/1999-09/2002 Chairperson, Nebraska LSG/LN-CLL Task Force

10/1997-09/2002 Chairperson, Autoimmune Diseases Transplantation Group, University of Nebraska Medical Center.

August 5, 1999 “The Evolving Role of Hematopoietic Stem Cell Transplantation for B-Cell Chronic Lymphocytic Leukemia”. University of Arizona, Scottsdale, Arizona.

August 6, 1999	“The Evolving Role of Hematopoietic Stem Cell Transplantation for B-Cell Chronic Lymphocytic Leukemia”. University of Arizona, Tucson, Arizona.
04/1999	Treatment Strategies and Future Research in B-CLL, Session Chairman and Presenter.
1998	Nebraska Lymphoma Study Group/Lymphoma Network-Chronic Lymphocytic Leukemia (CLL) Task Force Meeting, Omaha, NE
07/1998-06/1999	UNMC Cancer Center, Annual Seed-Grants Review Committee.
1998	Scientific Review Committee, UNMC/Eppley Cancer Center
07/1997-10/2002	Session Chairperson, “Stem Cell Transplantation II”, Fifth Seminar: New Trends in the Treatment of Acute Leukemia, Dubrovnik, Croatia.
07/1997-06/2000	Director-Allogeneic Stem Cell Transplantation Conference, UNMC, weekly or bi-monthly CME accredited course.
06/1989	Director-Hematology-Pathology Conference, UNMC
1987 and 1989	Chair, First Symposium on Emergencies in Hematology, University of Zagreb School of Medicine, Zagreb, Croatia.
	Secretary General, "New Trends in the Treatment of Acute Leukemia", European School of Oncology and EORTC, Dubrovnik, Croatia.

Served and currently serving as PI and AI for numerous NCI intramural clinical protocols in the field of hematopoietic allogeneic transplantation, chronic graft-versus-host disease, CAR T-Cells and cellular immunotherapy. Full list is available upon request.