University of Split School of Medicine

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Clinical characterization and outcomes in Chronic Graft-Versus-Host Disease

DOCTORAL DISSERTATION

Split, May 2023

Acknowledgements

This work was done at the National Cancer Institute, National Institutes of Health (NIH), the NIH Clinical Center in Bethesda, Maryland, and at the University of Nebraska Medical Center in Omaha, Nebraska and in collaboration with many colleagues across academic medical centers in the United States and Europe including Croatia.

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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].

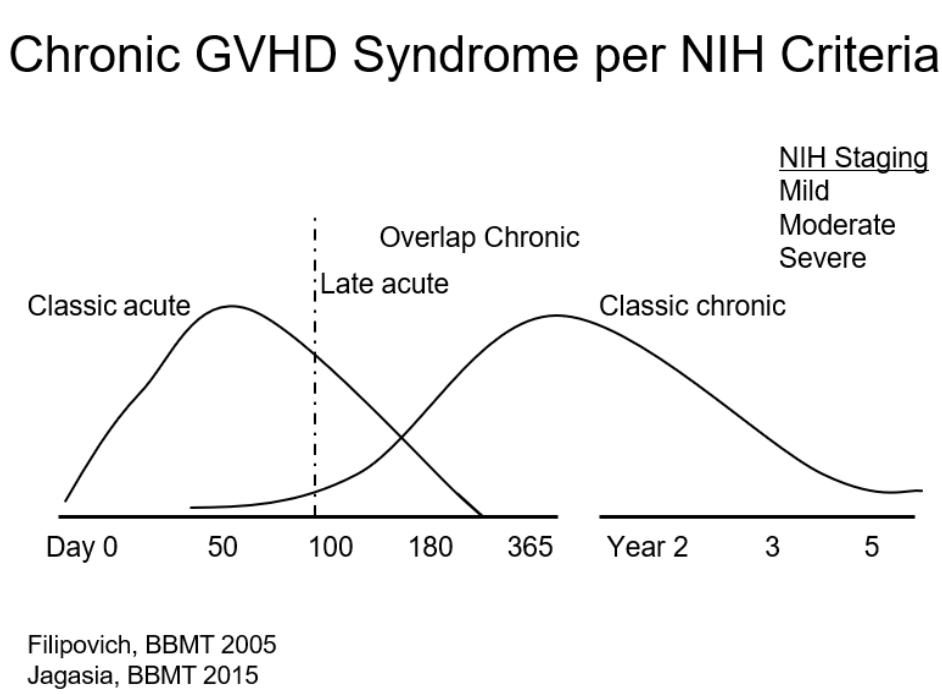

Figure 1. Chronic graft-versus-host disease timeline after infusion of allogeneic HSCT (NCI)

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].

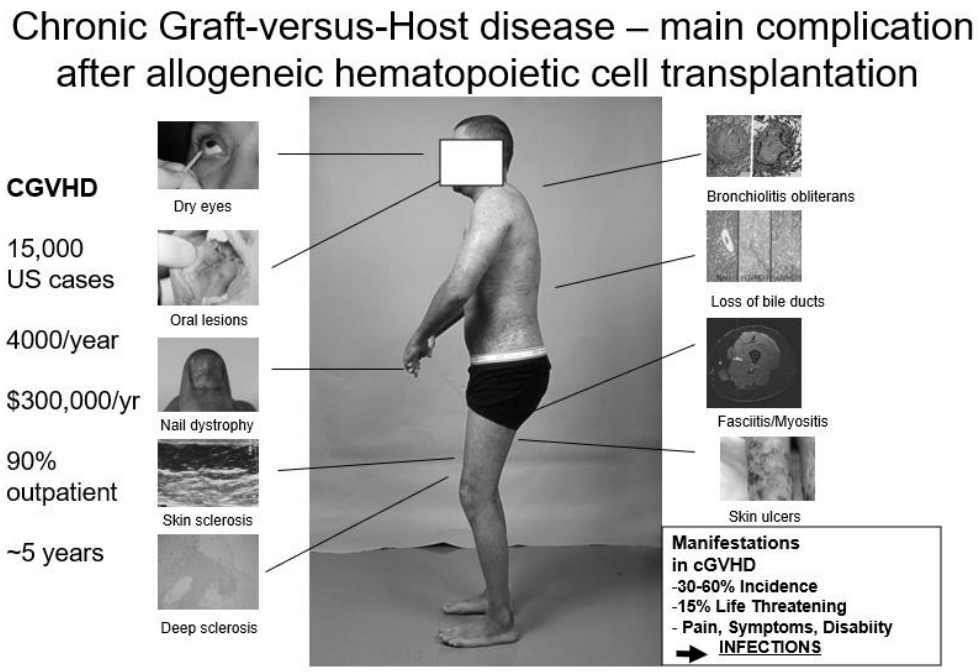

Figure 2. Manifestations of chronic graft-versus-host disease (NCI)

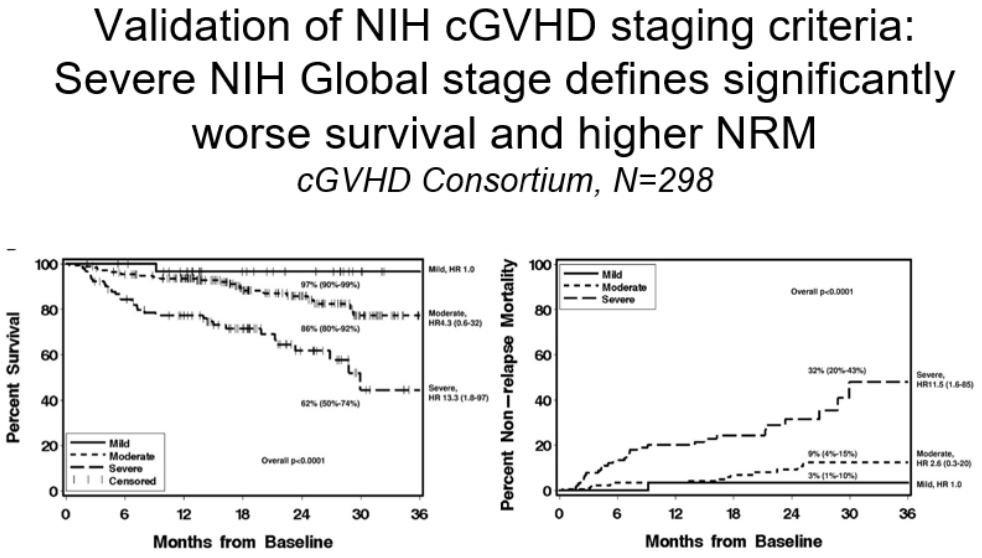

Figure 3. NIH severity scoring defines chronic GVHD severity predicts survival and transplant related mortality after allogeneic HSCT [7]

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 (IFNγ) 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 (TNFα).

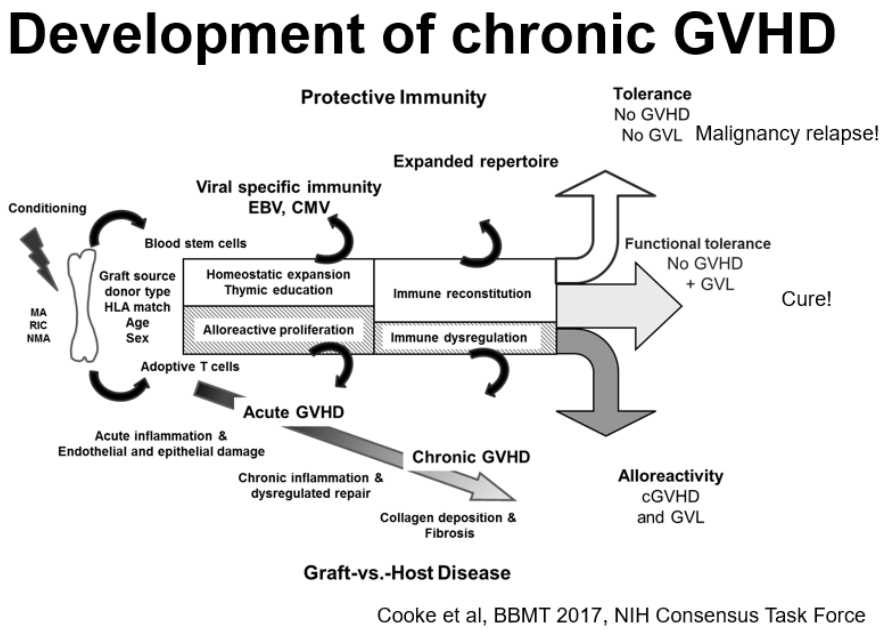

Figure 4. Pathophysiology of chronic graft-versus-host disease [13]

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.

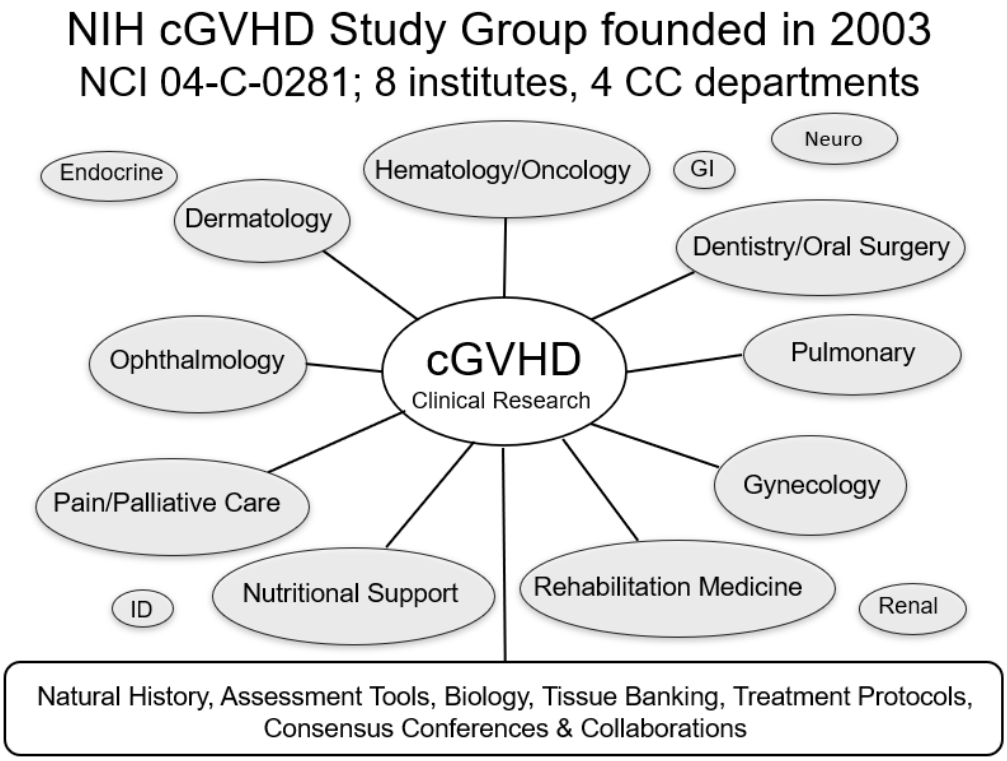

Figure 5. NIH Chronic GVHD Multidisciplinary Study Group Team Approach

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]) $x10^6$/kg and 30.1 x 22.0 +/- $x10^6$/kg in the TCD and M/C arms, respectively. The mean infused CD34+ cell doses were 2.0 +/- 1.8 $x10^6$/kg and 3.8 +/- 3.4 $x10^6$/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 αβ 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/m^2 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/m^2 on day 1 and 10 mg/m^2 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/m^2). 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*=.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*=.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.

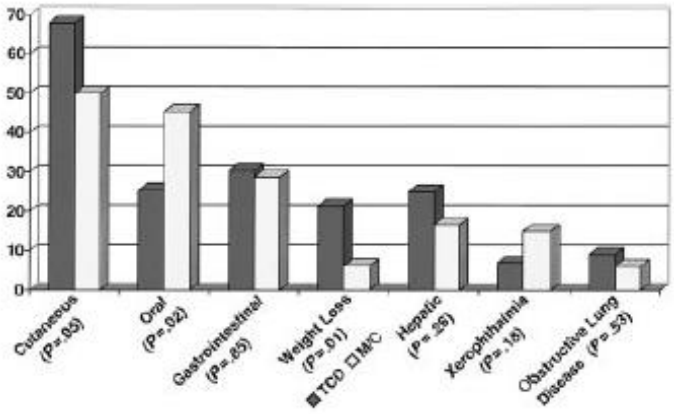

Figure 7. Chronic GVHD clinical manifestations at time of diagnosis.

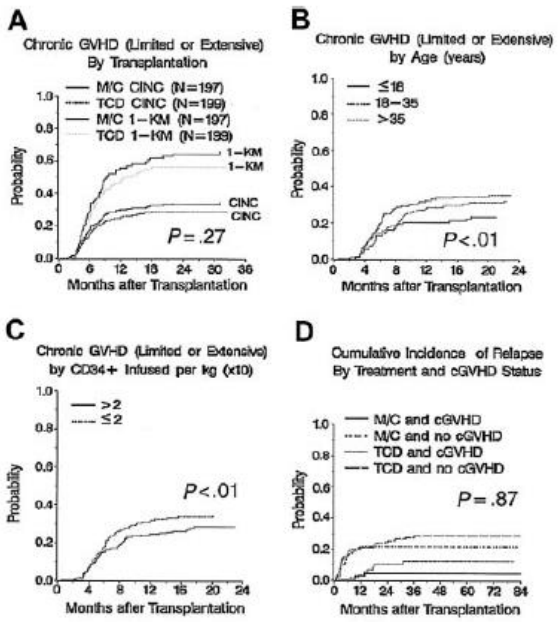

Figure 8. Cumulative incidence of chronic GVHD and relapse by covariates. (A) Cumulative incidence of chronic GVHD by treatment arm, P = 0.27. (B) Incidence of chronic GVHD by recipient age, P =0.01. (C) Incidence of chronic GVHD by CD34+ dose, P = 0.01. (D) Cumulative incidence of relapse by treatment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

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 alloHSCT 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 is randomized trials were 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/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.

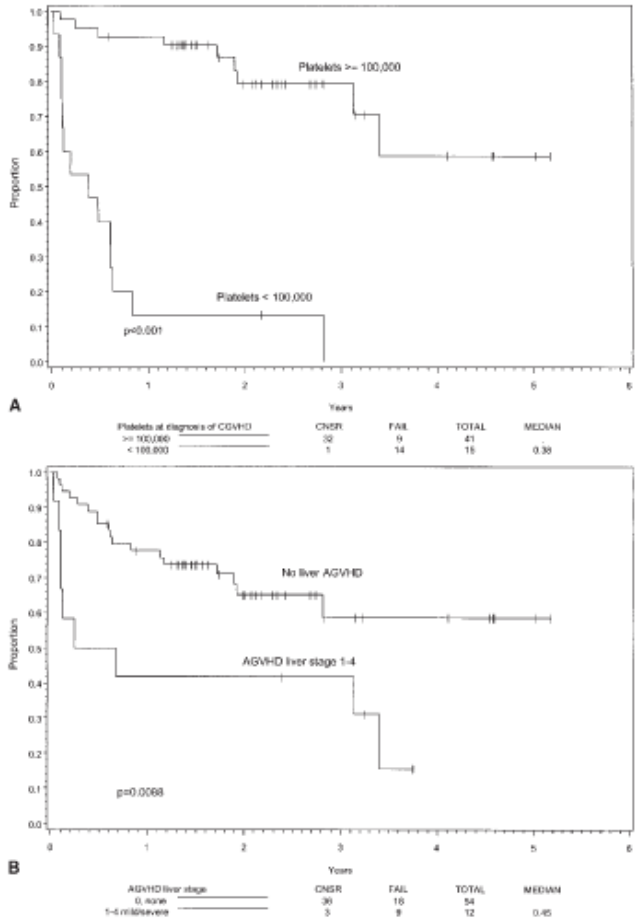

Figure 9. Survival following chronic GVHD after allogeneic blood stem-cell transplantation according to prognostic factors identified in the multivariate analysis. Only patients who developed cGVHD are included (n = 66). (A) Patients with more versus less than 100,000/mm^3 platelets at cGVHD diagnosis. (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 (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 ¼ none	58 (67%)	52 (69%)	0.74
1–4 ¼ mild/severe	29 (33%)	23 (31%)	
AGVHD liver stage: *n* (%)			
0 ¼ none	71 (82%)	61 (82%)	1.00
1–4 ¼ mild/severe	16 (18%)	13 (18%)	
AGVHD skin stage: *n* (%)			
0 ¼ none	39 (45%)	28 (37%)	0.34
1–4 ¼ mild/severe	48 (55%)	47 (63%)	
AGVHD upper GI stage: *n* (%)			
0 ¼ none	23 (26%)	24 (32%)	0.49
1–4 ¼ mild/severe	64 (74%)	51 (68%)	

[a]Patients at low risk of malignancy relapse were those with acute leukemia in first remission, chronic myelogeneous 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

	AlloPBSCT (*n* ¼ 87)		AlloBMT (*n* ¼ 75)	
Risk factor	RR (95% CI)	*P* value	RR (95% CI)	*P* 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

	AlloPBSCT (*n* ¼ 66)		AlloBMT (*n* ¼ 47)	
Risk factor	RR (95% CI)	*P* value	RR (95% CI)	*P* 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

	AlloPBSCT (*n* ¼ 87)		AlloBMT (*n* ¼ 75)	
Risk factor	RR (95% CI)	*P* value	RR (95% CI)	*P* 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.
[a]prognostic 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 c GVHD 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]	Mild-moderate-severe [12]
	0-10 severity scale [13]	0-10 severity scale [13]
	7-point change scale [14]	7-point change scale [14]
II. Chronic GVHD-nonspecific ancillary measures		
Function	Grip strength [15-17]	HAP [19]
	2-min walk time [18]	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
	Pruritus or itching	0-10 Scale	P
Eyes	Bilateral Schirmer's tear test scores without anesthesia	Mean of both eyes, mm	C
	Main ocular symptom at the time of the visit	0-10 Scale	P
Mouth	Erythema	Total score 0-15	C
	Lichen-type hyperkeratosis		C
	Ulcerations		C
	Mucoceles		C
	Symptoms of oral pain, dryness, sensitivity	0-10 Scale	P
Hematology	Platelet count	Number/μL	C
	Eosinophils	Percent	C
GI	Upper GI symptoms	0-3 Score	C
	Esophageal symptoms	0-3 Score	C
	Diarrhea	0-3 Score	C
Liver	Total serum bilirubin	mg/dL	C
	ALT, alkaline phosphatase	U/L	C
Lungs	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; FEV_1, 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.

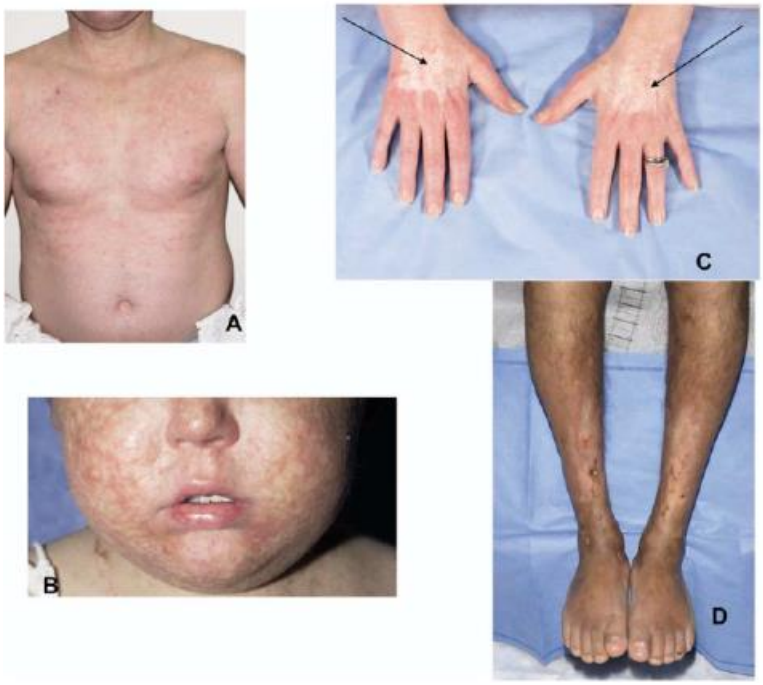

Figure 10. Skin manifestations for response to chronic GVHD. A erythematous papular rash, B erythematous rash with papules and small scaly plaques, C dermal sclerosis and D subcutanoues sclerosis

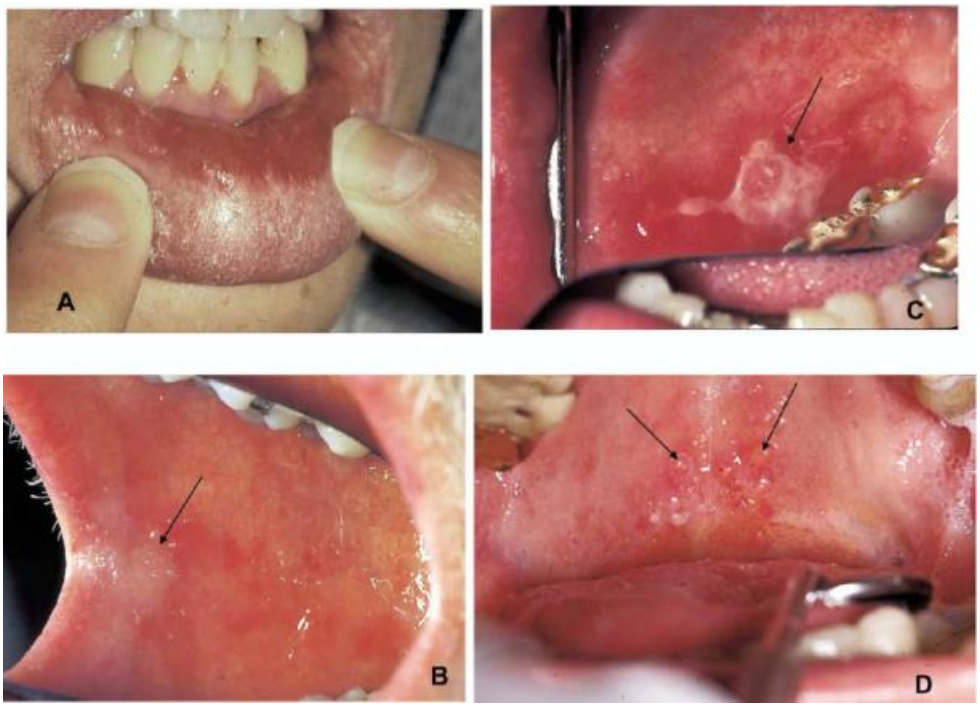

Figure 11. Oral manifestatiosn of GVHD. A moderate erythema, B sheet-like lichenoid hyperkeratosis, C ulcer with pseudomembranous fibrin exudates, and D mucoceles at the palate centre

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].

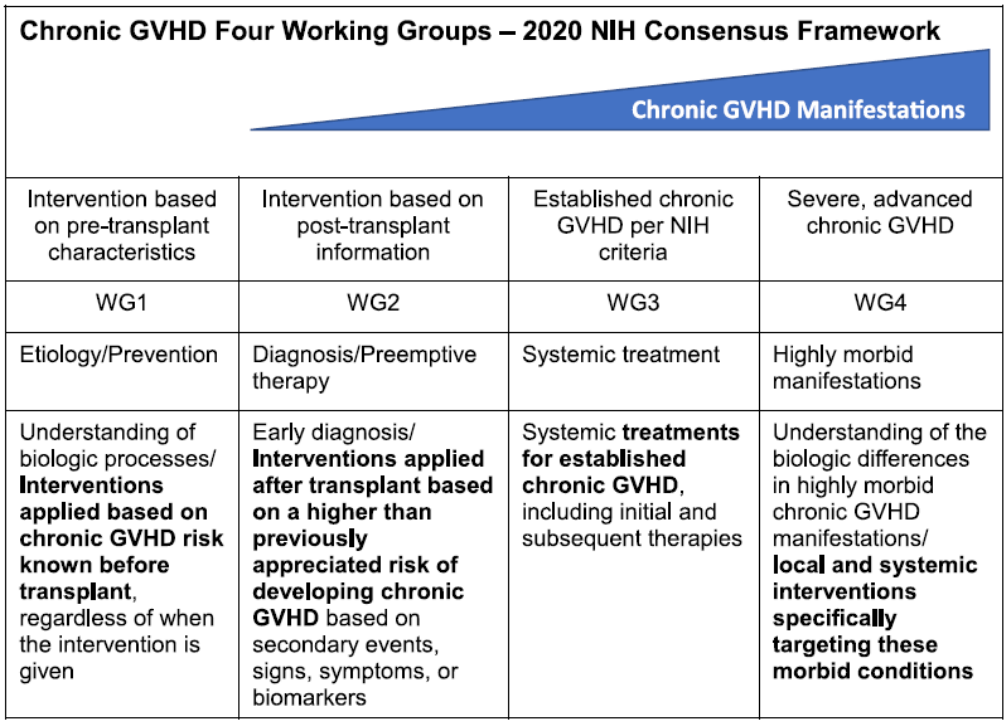

Figure 12. 2020 NIH Consensus Development Project on Criteria for Clinical Trials in Chronic GVHD working groups and their scopes.

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, L. 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.

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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.