HHS Public Access

Author manuscript

Bone Marrow Transplant. Author manuscript; available in PMC 2021 October 29.

Published in final edited form as:

Bone Marrow Transplant. 2021 July ; 56(7): 1584–1592. doi:10.1038/s41409-021-01211-2.

Predictors of Hematologic Malignancy Relapse in Patients with Advanced Chronic Graft-*versus*-Host Disease

Claire L. Ruben[1], **Filip Pirsl**[1], **Seth M. Steinberg**[2], **Noa G. Holtzman**[1], **Laura Parsons-Wandell**[1], **Judy Baruffaldi**[1], **Lauren M. Curtis**[1], **Sandra A. Mitchell**[3], **Ana Zelic Kerep**[1], **Edward W. Cowen**[4], **Ann Berger**[5], **Galen O. Joe**[6], **Manuel B. Datiles III**[7], **Jacqueline W. Mays**[8], **Steven Z. Pavletic**[1]

[1]Immune Deficiency Cellular Therapy Program, Center for Cancer Research, National Cancer Institute, National Institutes of Health, 9000 Rockville Pike, Building 10, Room CRC 4-3130, Bethesda, MD 20892

[2]Biostatistics and Data Management Section, National Cancer Institute, National Institutes of Health, 9609 Medical Center Drive, Room 2W334, Rockville, MD 20850

[3]Outcomes Research Branch, Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health, 9609 Medical Center Drive MSC 9764, Bethesda, MD 20892

[4]Dermatology Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, 9000 Rockville Pike, Building 10, Room 12N240A, Bethesda, MD 20892

[5]Pain and Palliative Care Service, National Institutes of Health Clinical Center, National Institutes of Health, 10 Center Drive, Bethesda, MD 20892

[6]Rehabilitation Medicine Department, National Institutes of Health Clinical Center, National Institutes of Health, 10 Center Drive, Bethesda, MD 20892

[7]National Eye Institute, National Institutes of Health, 31 Center Drive, Building 31, MSC 2510, Bethesda, MD 20892

[8]Oral Immunobiology Unit, National Institute of Dental and Craniofacial Research, National Institutes of Health, 30 Convent Drive, Building 30 Room 301, MSC 4340, Bethesda, MD 20892

Abstract

Malignancy relapse remains a major barrier to treatment success in patients after allogeneic hematopoietic stem cell transplantation (allo-HSCT). Chronic graft-versus-host disease (cGVHD) markedly reduces hematologic malignancy relapse risk, but relapses still occur in these patients.

Corresponding Author: **Steven Z. Pavletic, MD**, Immune Deficiency Cellular Therapy Program, Head, Graft-versus-Host and Late Effects Section, National Cancer Institute, Center for Cancer Research, 10 Center Drive, Room CRC 4-3130, Bethesda, MD 20892-1907, USA, pavletis@mail.nih.gov.

Competing Interests

The authors have no competing financial interests in relation to the work.

Patients (n=275) with moderate or severe cGVHD were enrolled on the National Cancer Institute (NCI) prospective cross-sectional natural history study (NCT00092235). Subjects were median 36 months after allo-HSCT and were followed subsequently for malignancy relapse and survival.

Seventeen patients experienced relapse. In a multivariable model including time-dependent influences on relapse, risk factors associated with increased risk of relapse included shorter time from transplant to cGVHD evaluation (HR 0.279, 95% CI 0.078-0.995) and lower number of prior lines of systemic immunosuppressive therapy for cGVHD (HR 0.260, 95% CI 0.094-0.719). In a model excluding time-dependent influences on relapse risk, lower number of prior lines of systemic immunosuppressive therapy for cGVHD (HR 0.288, 95% CI 0.103-0.804), lower C4 complement level (HR 0.346, 95% CI 0.129-0.923), and higher body mass index (HR 3.222, 95% CI 1.156-8.974), were all associated with increased relapse risk.

Parameters indicating cGVHD severity and activity are associated with risk of malignancy relapse. Classical predictors of relapse after allo-HSCT do not seem to be prognostic.

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) provides prospect of cure for many patients with high-risk or treatment-refractory hematologic malignancies.[1,2] Treatment success depends upon the maximization of anti-neoplastic graft-versus-tumor (GVT) effects as well as the control of systemic alloreactivity often associated with severe complications, most notably chronic graft-versus-host disease (cGVHD).[3,4]

Chronic GVHD is a clinically significant late effect of allo-HSCT in which donor T-cells mount an immunologic reaction against host tissues recognized as foreign. Manifestations affecting the skin, mouth, eyes, lungs, joints and fascia, gastrointestinal (GI) tract, genitals, and liver compromise organ function and affect 30-50% of transplant recipients. cGVHD is the leading cause of non-relapse morbidity and mortality among allo-HSCT recipients.[5,6]

Although control of transplant complications, including infection and acute and chronic GVHD, has greatly improved, incidence of relapse following allo-HSCT has seen only marginal declines over the last two to three decades.[7] Furthermore, patients who relapse after transplant have a poor prognosis,[8] with variability in outcome depending on patient age,[9] malignancy type, time from allo-HSCT to relapse, disease burden, and conditions of first transplant.[10] Most relapses occur within the year immediately following transplant,[10] and little information is available regarding relapse outside of this timeframe, especially as it pertains to patients with established cGVHD.

Chronic GVHD has been repeatedly associated with markedly decreased risk of malignancy relapse after allo-HSCT.[11,12,13]

Nevertheless, relapse remains a prominent cause of death also for patients with cGVHD years following transplant. Why hematologic malignancy escapes cGVHD related graft-versus tumor effects is not understood. Research addressing relapse risk factors in the context of severe cGVHD is scarce. The aim of this study is to advance understanding of factors determining risk of malignancy recurrence in patients with advanced cGVHD who

survive to extended time points from allo-HSCT using long-term follow-up of a clinically highly annotated patient cohort.

Subjects and Methods

Patient Selection and Characteristics

Patients were consented and enrolled on the NCI Chronic Graft-Versus-Host Disease Natural History Study (NCT00092235) and presented for a comprehensive, one-week evaluation by subspecialists in dentistry, dermatology, gynecology, ophthalmology, pain and palliative care, rehabilitation medicine, and hematology/oncology. Evaluation was conducted in accordance with the 2005 NIH cGVHD diagnostic and staging criteria.[14] Relapse data were collected during an annual follow-up survey of patients or from referring physicians.

A total of 412 patients were enrolled between October 2004 and December 2017. Patients found not to have cGVHD upon evaluation (n=22), patients with missing records (n=1), patients who received HSCT for a non-malignant disease (n=26), patients who relapsed after HSCT but prior to cGVHD evaluation (n=66), and patients lost to follow-up (n=22) were excluded, resulting in a cohort of 275 patients for analysis. Eight deceased patients with unknown causes of death were censored as alive and relapse-free at last date of follow-up for analysis.

Potential predictors of malignancy relapse included patient demographic factors and measures of cGVHD activity and severity (Table 1, Table 2). Patient demographics included sex, age at evaluation, and body mass index (BMI) calculated at evaluation. Transplant- and treatment-related variables included indication for transplant, disease status at transplant (complete remission (CR) or other (minimal disease, progressive disease, residual disease, or partial response)), type of conditioning regimen (myeloablative (MAC)/non-myeloablative (nMAC)), total body irradiation (TBI), donor relationship (related/unrelated), stem cell source (peripheral blood, bone marrow, or umbilical cord), T-cell depletion, human leukocyte antigen (HLA) match (match/mismatch), donor sex, donor and recipient cytomegalovirus (CMV) IgG status, time from transplant to NIH cGVHD evaluation, time from transplant to cGVHD diagnosis, and time from cGVHD diagnosis to NIH cGVHD evaluation. Measures of cGVHD activity and severity included NIH cGVHD global score, individual NIH organ scores [ocular, gastrointestinal tract, joints and fascia, liver, lungs, oral, skin, genitals (females only)], number of organs affected by cGVHD, prior acute GVHD, number of systemic immunosuppressive therapies (IST) for cGVHD prior to NIH evaluation, and intensity of immunosuppression at the time of evaluation (defined per Mitchell et al. as none, mild = single-agent prednisone <0.5mg/kg/day, moderate = prednisone ≥ 0.5mg/kg/day and/or any single agent/modality, and high = 2 or more agents/modalities ± prednisone ≥ 0.5mg/kg/day).[15]

Statistical Analysis

Overall survival was determined from the on-study date until date of death or last follow-up using the Kaplan-Meier method. Progression-free survival was determined from the on-study date until date of relapse, death without prior relapse, or last follow-up. The

cumulative incidence of relapse, with death treated as a competing risk, was estimated using the method of Gooley.[16]

Potential predictors of malignancy relapse were evaluated in univariate analysis. When factors were assessed for their association with the cumulative incidence of relapse, differences in cumulative incidence were assessed using Gray's test. Multi-group factors were subsequently combined into two groups to evaluate the association with the cumulative incidence, and p-values were adjusted by multiplying the unadjusted p-value by the number of implicit tests which would be performed to arrive at the grouping. Parameters in univariate analysis with $p < 0.10$ were added to a Cox proportional hazards model with stepwise selection to estimate their joint effect on relapse.

An additional Cox proportional hazards model that excluded time-dependent influences on relapse was similarly formulated to estimate non-temporal factors that could potentially contribute to relapse risk.

Results

Patients

Two hundred seventy-five patients were included in the analysis (55% men, 45% women). Median age at NIH cGVHD evaluation was 48 years, (IQR, 35-57 years) and median age at transplant was 44 years (IQR, 31-53 years). The most common indications for transplant were acute leukemia or myelodysplastic syndrome (n=151, 55%) followed by lymphoma (n=63, 23%) (Table 1).

Most patients received a related donor transplant (n=154, 56%) and more patients received peripheral blood (n=216, 79%) than either bone marrow (n=53, 19%) or umbilical cord (n=6, 2%) stem cells. Forty-four patients (16%) were transplanted from an HLA mismatched donor. Fewer patients underwent nMAC (n=115, 42%) than MAC (n=160, 58%). Fifty patients (18%) received some form of T-cell depletion at transplant. Most patients (n=164, 60%) did not receive TBI with transplant conditioning. Half of all patients had residual or progressive disease at transplant (n=138, 50%) while slightly less than half were in complete remission (n=131, 48%) with the remaining patients (n=6, 2%) possessing unknown disease status.

The median time from transplant to cGVHD diagnosis was seven months (IQR, 5-12) (Table 2). Patients were enrolled on study at a median of 36 months (IQR, 22-58) post-transplant and 24 months post-cGVHD diagnosis (IQR, 11-49). Patients had a median of five organs (IQR, 4-6) affected by cGVHD at evaluation. Median NIH average organ score was 1.13 (IQR, 0.75-1.43). Most patients were enrolled with severe (n=194, 71%) or moderate cGVHD (n=75, 27%) per NIH global score. cGVHD manifestations of the skin (n=217, 79%) and eyes (n=218, 79%) were most frequent. Skin was the organ most frequently affected by severe cGVHD (n=123, 56%). Acute GVHD was seen in most (n=188, 68%) patients prior to their cGVHD diagnosis. Patients received a median of four systemic IST (IQR 2-5 treatments) for cGVHD prior to NIH evaluation. Most patients were receiving

moderate (n=104, 38%) or high (n=111, 40%) intensity immunosuppressive regimens at study consent.[15]

Relapse

Seventeen patients experienced relapse (diagnoses: multiple myeloma – 4, acute myeloid leukemia – 3, acute lymphoblastic leukemia – 3, Hodgkin lymphoma – 3, chronic lymphocytic leukemia – 3; includes one transformation to diffuse large B-cell lymphoma, and chronic myelogenous leukemia – 1). The 48- and 60-month cumulative incidences of relapse were 5.7% (95% CI: 3.3, 8.9%) and 6.2% (95% CI: 3.7, 9.6%), respectively (Figure 1). Relapses occurred at a median of 13.7 months after study enrollment, with all relapses occurring between 1.2- and 104-months post enrollment. Five- and ten-year overall survival were 73.9% (95% CI: 66.8, 77.9%) and 63.6% (95% CI: 55.6, 70.6%), respectively. Five- and ten-year progression-free survival were 70.5% (95% CI: 64.3, 75.8%) and 59.9% (95% CI: 51.6, 67.3%), respectively (Figure 2). At last follow-up 10 of 17 patients who experienced relapse had died.

Predictors

By Gray's test, patients with a shorter time from transplant to study consent (<35.5 months vs. ≥ 35.5 months, p=0.018) were at increased risk of relapse, as were patients with a shorter time from cGVHD diagnosis to study consent (<24 vs. ≥ 24 months., p=0.019). Risk of relapse was higher for patients who had received two or fewer prior systemic IST for cGVHD compared to those who had received three or more such therapies (p<0.0010) (Figure 3). Patients with lower C4 complement level (defined as <23 mg/dL) were more likely to relapse than those with higher C4 complement level (≥23 mg/dL; p=0.027) (Figure 4). Obese body mass index (BMI of >30) also placed patients at an elevated risk of relapse (obese vs. other, p=0.023) (Figure 5). Intensity of immunosuppression (p=0.058) and global cGVHD severity (moderate vs. severe, p=0.09) were inversely associated with risk of relapse but to a lesser degree. A description of the potential predictors displayed according to their relapse status as of the date of analysis, as well the p-value for the trait with respect to its association with cumulative incidence of relapse is presented in Table 3. Notable parameters found not to have an association with malignancy relapse in univariate analysis included use of TBI at transplant, T-cell depleted graft, myeloablative conditioning, disease status at transplant, degree of HLA match between donor and recipient, female donor to male recipient, and blood vs. marrow stem cell source.

Multivariable Cox hazards analysis with stepwise selection produced a model using shorter time from transplant to NIH cGVHD evaluation (HR 0.279, 95% CI 0.078-0.995) and lower number of prior lines of systemic immunosuppressive therapy for cGVHD (HR 0.260, 95% CI 0.094-0.719) to predict malignancy relapse (Table 4). In an additional Cox model excluding time-dependent influences on relapse risk, lower number of prior lines of systemic immunosuppressive therapy for cGVHD (HR 0.288, 95% CI 0.103-0.804), lower C4 complement level (HR 0.346, 95% CI 0.129-0.923), and higher body mass index (HR 3.222, 95% CI 1.156-8.974), were all associated with increased relapse risk (Table 5).

Discussion

In this analysis of patients severely affected with cGVHD 60-month cumulative incidence of relapse (6.2%) was relatively low compared to what is usually expected in patients without cGVHD.[12] While risk of relapse is dependent upon a multitude of disease and transplant-related factors, incidence of relapse determined by this analysis nonetheless supports associations between cGVHD and strong GVT effect,[17,18,19] while also indicating that relapse remains a serious complication for transplant patients even if they develop cGVHD.

Patients were enrolled at a median of 36 months post-transplant and all had established, advanced cGVHD. Yet the observation that patients with a longer time course from transplant to NIH cGVHD evaluation were at decreased risk of relapse supports the notion that relapse is generally an early event in the post-transplant course (<12 months), and likelihood of relapse decreases with increasing time from transplant.[20,21,22] The date of study enrollment marks a unifying timepoint at which all patients presented to the NIH with established cGVHD. Although these patients differ in their time from transplant and/or cGVHD diagnosis, the goal of the study was to determine relapse from date of study enrollment assuring that all patients in this cohort could be evaluated for impact of cGVHD manifestations at the time of presentation.

Patients who received a greater number of systemic IST were likewise at reduced relapse risk. It can be inferred that the number of systemic IST administered prior to cGVHD evaluation is representative of cGVHD severity and duration. Patients receiving a greater number of therapies have failed multiple lines of treatment for cGVHD over an extended time course from transplant. A high number of prior therapies also indicates the presence of treatment-refractory disease. Thus, the number of prior systemic IST is a surrogate for both duration and severity of cGVHD, suggesting a positive relationship between cGVHD severity and enhanced GVT effects.[12]

As time from transplant is a well-known primary driver in determining relapse risk,[10] an additional Cox hazards analysis that excluded time-dependent metrics produced a final model defining three parameters associated with increased risk of relapse. In addition to lower number of prior lines of systemic IST for cGVHD, obese body mass index (BMI of >30) also placed patients at an elevated risk of relapse as compared to non-obese patients. High BMI has previously been correlated with increased incidence of leukemia, multiple myeloma, and non-Hodgkin lymphoma,[23] and this finding warrants further investigation. Lower C4 complement level, an established parameter of cGVHD activity,[24] also indicated elevated relapse risk. Thus, lower C4 levels coinciding with heightened relapse risk further supports the possible positive relationship between cGVHD severity and enhanced GVT effects.[12]

Importantly, several classic relapse risk factors were not predictive in this cohort of transplant recipients who were all enrolled on study late after transplant (>22 months). While TBI,[25] T-cell depletion,[26] residual disease at transplant,[27] degree of HLA match between donor and recipient,[28] female donor to male recipient,[29] and a myeloablative

conditioning regimen[30] have been shown to reduce relapse risk in transplant recipients, no such associations were observed in this study. Because T-cell depletion reduces risk of GVHD, it is potentially underrepresented within the study population, although use was documented in 18% of patients enrolled. It is also possible that increased risk of relapse conferred by T-cell depletion may have been compromised due to the presence of cGVHD itself.

Loss of the HLA alloantigen expression is a recognized mechanism of tumor immune escape after allo-HSCT[31] and accounts for up to one third of relapses after haploidentical transplant.[32] Similarly, loss and/or mutation of tumor target antigen is likewise associated with poor outcomes, even in patients without genomic loss of HLA.[33] It is possible that GVT effects associated with cGVHD may favor immune evasion by placing increased immune pressure on relapsing cells. Thus, antigenic loss and mutation of target antigens may possibly explain the abrogation of standard pre-transplant prognostic factors observed in this study of patients with moderate or severe cGVHD who are late after transplant, although further testing of this hypothesis is required.

To our knowledge, this is the first long-term follow-up study examining malignancy relapse in a population consisting entirely of patients already affected by cGVHD. This study highlights the fact that malignancy relapse is also a notable complication in such patients, as only 7 of the 17 relapsing patients were alive upon last follow-up. While previous analyses have assessed the effect of cGVHD on relapse incidence as a surrogate of GVT, this study provides detailed analysis of possible factors affecting relapse in cGVHD patients by examining transplant-specific and cGVHD-specific measures and clinical characteristics according to NIH criteria. These findings suggest that risk factors for relapse among patients late after transplant with moderate or severe cGVHD may substantially differ from those of the overall transplant population. Chronic immune dysregulation characteristic of cGVHD may contribute to immunological differences between cGVHD patients and other recipients of allo-HSCT that ultimately determine risk of relapse.

This study has some limitations. Due to the cross-sectional study design, cGVHD patients were evaluated only once in the clinic and subsequently followed only for relapse and survival. Therefore, this study was not designed to monitor and assess cGVHD activity and severity over time. It is possible that timing of symptom flares, therapeutic interventions, and other temporal factors may be important in the pathophysiology of relapse. Longitudinal monitoring of these factors may result in a more complete picture of disease course. Additionally, non-GVHD controls were not available for concurrent comparison. This study was not intended to examine incidence of relapse in the transplant population at large, but instead to investigate relapse risk amongst patients with established cGVHD who survive to extended timepoints from transplant.

It is believed that aggressive malignancies are generally less susceptible to GVT due in part to rapid proliferation rates that enable growth before full establishment of anti-neoplastic activity.[10,34] Yet when malignancies were dichotomized in this study based upon relative relapse risk (low/intermediate risk [CML, IMF, MPD, CLL, NHL, HL] vs. high/very high risk [AML, ALL, MDS, MM, Ewing’s sarcoma]) relapse incidence was almost

identical, suggesting potent GVT effects across disease entities. Future studies might use a standardized measure of disease risk such as Armand and colleagues' Disease Risk Index[35], which is based on cytogenetic and other disease specific information that was not available for patients on this study.

It should be noted that the number of observed relapses was relatively small (n=17), which is consistent with most patients being enrolled having severe cGVHD (70.5%) and being quite late after transplant (a median of 36 months post allo-HSCT). Patients with disease progression or death soon after transplant were not the focus of this analysis, as this study aimed to analyze the understudied population of transplant recipients with severe cGVHD who survive to extended time points post allo-HSCT. Future studies might examine relapse trends encompassing cGVHD patients earlier after transplant.

In conclusion, these results show that classic risk factors for malignancy relapse after allo-HSCT are not prognostic in patients with clinically manifested moderate or severe cGVHD who are late after transplant. Parameters indicating cGVHD severity and activity are associated with risk of malignancy relapse. Relationship of higher BMI and risk of relapse needs to be further investigated.

These findings obtained in a large cohort of patients severely affected with cGVHD indicate the need for developing novel relapse prevention strategies for this patient population.

Acknowledgements

The authors have no conflicts of interest to disclose. The authors would like to thank all patients and their families for participating in the NIH cGVHD natural history study. This work was supported by the Intramural Research Program of the National Institutes of Health, Center for Cancer Research, National Cancer Institute; the National Institute for Dental and Craniofacial Research; the National Institute of Arthritis and Musculoskeletal and Skin Diseases; and the National Eye Institute. The views expressed in this work do not represent the official views of the National Institutes of Health or the United States Government.

References

1. Singh Anurag K, McGuirk Joseph P. Allogeneic Stem Cell Transplantation: A Historical and Scientific Overview. Cancer research. 2016;76:6445–6451. [PubMed: 27784742]
2. Koreth J, Schlenk R, Kopecky KJ, Honda S, Sierra J, Djulbegovic BJ, et al. Allogeneic Stem Cell Transplantation for Acute Myeloid Leukemia in First Complete Remission: Systematic Review and Meta-analysis of Prospective Clinical Trials. JAMA. 2009;301(22):2349–2361. [PubMed: 19509382]
3. Choi SW, Reddy P. Current and emerging strategies for the prevention of graft-versus-host disease. Nature reviews Clinical oncology. 2014;11(9):536–47.
4. Li JM, Giver CR, Lu Y, Hossain MS, Akhtari M, Waller EK. Separating graft-versus-leukemia from graft-versus-host disease in allogeneic hematopoietic stem cell transplantation. Immunotherapy. 2009;1(4):599–621. [PubMed: 20191089]
5. Arai S, Arora M, Wang T, Spellman SR, He W, Couriel DR, et al. Increasing incidence of chronic graft-versus-host disease in allogeneic transplantation: a report from the Center for International Blood and Marrow Transplant Research. Biol Blood Marrow Transplant. 2015; 21(2): 266–74. [PubMed: 25445023]
6. Martin PJ, Counts GW Jr, Appelbaum FR, Lee SJ, Sanders JE, Deeg HJ, et al. Life expectancy in patients surviving more than 5 years after hematopoietic cell transplantation. J Clin Oncol 2010;28(6):1011–1016. [PubMed: 20065176]

7. Bishop MR, Alyea EP 3rd, Cairo MS, Falkenburg JHF, June CH, Kroger N, et al. Introduction to the reports from the National Cancer Institute First International Workshop on the Biology, Prevention, and Treatment of Relapse after Allogeneic Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant. 2010;16(5):63–564.
8. Mo XD, Kong J, Zhao T, Xu LP, Zhang XH, Liu DH, et al. Extramedullary relapse of acute leukemia after haploidentical hematopoietic stem cell transplantation: incidence, risk factors, treatment, and clinical outcomes. Biol Blood Marrow Transplant. 2014; 20(12): 2023–2028. [PubMed: 25196855]
9. Schmid C, Labopin M, Nagler A, Bornhauser M, Finke J, Fassas A, et al. Donor lymphocyte infusion in the treatment of first hematological relapse after allogeneic stem-cell transplantation in adults with acute myeloid leukemia: A retrospective risk factors analysis and comparison with other strategies by the EBMT Acute Leukemia Working Party. J. Clin. Oncol. 2007;25:4938–4945. [PubMed: 17909197]
10. Barrett AJ, Battiwalla M. Relapse after allogeneic stem cell transplantation. Expert review of hematology. 2010;3(4):429–441. [PubMed: 21083034]
11. Signori A, Crocchiolo R, Oneto R, Sacchi N, Sormani M, Fagioli F, et al. Chronic GVHD is associated with inferior relapse risk irrespective of stem cell source among patients receiving transplantation from unrelated donors. Bone Marrow Transplantation. 2012; 47(11):1474–1478. [PubMed: 22465976]
12. Stern M, de Wreede LC, Brand R, van Biezen A, Dreger P, Mohty M, et al. Sensitivity of hematological malignancies to graft-versus-host effects: an EBMT megafile analysis. Leukemia. 2014;28(11):2235–2240. [PubMed: 24781016]
13. Gratwohl A, Brand R, Apperley J, van Biezen A, Bandini G, Devergie A, et al. Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation (CLWP-EBMT). Graft-versus-host disease and outcome in HLA-identical sibling transplantations for chronic myeloid leukemia. Blood. 2002;100(12):3877–3886. [PubMed: 12433695]
14. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant 2005;11(12):945–56. [PubMed: 16338616]
15. Mitchell SA, Leidy NK, Mooney KH, Dudley WN, Beck SL, LaStayo PC, et al. et al. Determinants of functional performance in long-term survivors of allogeneic hematopoietic stem cell transplantation with chronic graft-versus-host disease. Bone Marrow Transplant. 2010;45:762–769. [PubMed: 19784078]
16. Gooley TA, Leisinring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Statistics in Medicine 1999; 18: 695–706. [PubMed: 10204198]
17. Miflin G, Russell NH, Franklin I, Cook G, Milligan DW, Hutchinson RM, et al. An analysis of the effect of chronic GvHD on relapse and survival following allogeneic PBSC transplantation. Cytotherapy. 2000;2(6):423–428. [PubMed: 12044222]
18. Brunet S, Urbano-Ispizua A, Ojeda E, Ruiz D, Moraleda M, Diaz A, et al. Evidence of graft-versus-tumor (GVT) effect in 136 patients with advanced hematologic malignancies receiving unmanipulated peripheral blood stem cell allografts (allo-PSCT): the Spanish experience. Blood. 1999;94:165a
19. Lee SJ, Klein JP, Barrett AJ, Ringden J, Antin JH, Cahn JY, et al. Severity of chronic graft-versus-host disease: association with treatment-related mortality and relapse. Blood. 2002;100(2):406–414. [PubMed: 12091329]
20. Preisler HD, Anderson K, Rai K, Cuttner J, Yates J, DuPre E, et al. The frequency of long- term remission in patients with acute myelogenous leukaemia treated with conventional maintenance chemotherapy: a study of 760 patients with a minimal follow-up time of 6 years. British journal of haematology. 1989;71(2):189–194. [PubMed: 2923805]
21. Schiffer CA, Dodge R, Larson RA. Long-term follow-up of Cancer and Leukemia Group B studies in acute myeloid leukemia. Cancer. 1997;80:2210–2214. [PubMed: 9395036]
22. Boyiadzis M, Arora M, Klein JP, Hassebroek A, Hemmer M, Urbano-Ispizua A, et al. Impact of chronic graft-versus-host disease on late relapse and survival on 7,489 patients after myeloablative

allogeneic hematopoietic cell transplantation for leukemia. Clin Cancer Res. 2015;21(9):2020–2028. [PubMed: 25348512]

23. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet. 2008;371(9612):569–578. [PubMed: 18280327]
24. Grkovic L, Baird K, Steinberg SM, Williams KM, Pulanic D, Cowen EW, et al. Clinical laboratory markers of inflammation as determinants of chronic graft-versus-host disease activity and NIH global severity. Leukemia. 2012;26(4):633–643. [PubMed: 22005783]
25. Page KM, Labopin M, Ruggeri A, Michel G, Diaz de Heredia C, O"Brien T, et al. Factors Associated with Long-Term Risk of Relapse after Unrelated Cord Blood Transplantation in Children with Acute Lymphoblastic Leukemia in Remission. Biol Blood Marrow Transplant. 2017;23(8):1350–1358. [PubMed: 28438676]
26. Soiffer RJ, Lerademacher J, Ho V, Kan F, Artz A, Champlin RE, et al. Impact of immune modulation with anti-T-cell antibodies on the outcome of reduced-intensity allogeneic hematopoietic stem cell transplantation for hematologic malignancies. Blood. 2011;117(25):6963–6970. [PubMed: 21464372]
27. Bader P, Hancock J, Kreyenberg H, Goulden NJ, Niethammer D, Oakhill A, et al. Minimal residual disease (MRD) status prior to allogeneic stem cell transplantation is a powerful predictor for post-transplant outcome in children with ALL. Leukemia 2002; 16: 1668–1672. [PubMed: 12200679]
28. Brunstein CG, Petersdorf EW, DeFor TE, Noreen H, Maurer D, MacMillan ML, et al. Impact of allele-level HLA mismatch on outcomes in recipients of double umbilical cord blood transplantation. Biol Blood Marrow Transplant. 2016;22:487–492. [PubMed: 26431630]
29. Kongtim P, Di SA, Rondon G, Chen J, Adekola K, Popat U, et al. Can a female donor for a male recipient decrease the relapse rate for patients with acute myeloid leukemia treated with allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2015;21:713–9. [PubMed: 25540936]
30. Pérez-Simón JA, Díez-Campelo M, Martino R, Brunet S, Urbano A, Caballero MD, et al. Influence of the intensity of the conditioning regimen on the characteristics of acute and chronic graft-versus-host disease after allogeneic transplantation. Br J Haematol. 2005;130(3):394–403. [PubMed: 16042689]
31. Vago L, Perna SK, Zanussi M, Mazzi B, Barlassina C, Lupo Stanghellini MT, et al. Loss of mismatched HLA in leukemia after stem-cell transplantation. N Engl J Med. 2009;361(5):478–488. [PubMed: 19641204]
32. Crucitti L, Crocchiolo R, Toffalori C, Mazzi B, Greco R, Signori A, et al. Incidence, risk factors and clinical outcome of leukemia relapses with loss of the mismatched HLA after partially incompatible hematopoietic stem cell transplantation. Leukemia. 2015;29(5):1143–1152. [PubMed: 25371177]
33. Toffalori C, Zito L, Gambacorta V, Riba M, Oliveira G, Bucci G, et al. Immune signature drives leukemia escape and relapse after hematopoietic cell transplantation. Nat Med. 2019; 25, 603–611. [PubMed: 30911134]
34. Kolb HJ. Graft-versus-leukemia effects of transplantation and donor lymphocytes. Blood. 2008; 112:4371–4383. [PubMed: 19029455]
35. Armand P, Kim HT, Logan BR, Wang Z, Alyea EP, Kalaycio ME, et al. Validation and refinement of the Disease Risk Index for allogeneic stem cell transplantation. Blood 2014; 123: 3664–3671. [PubMed: 24744269]

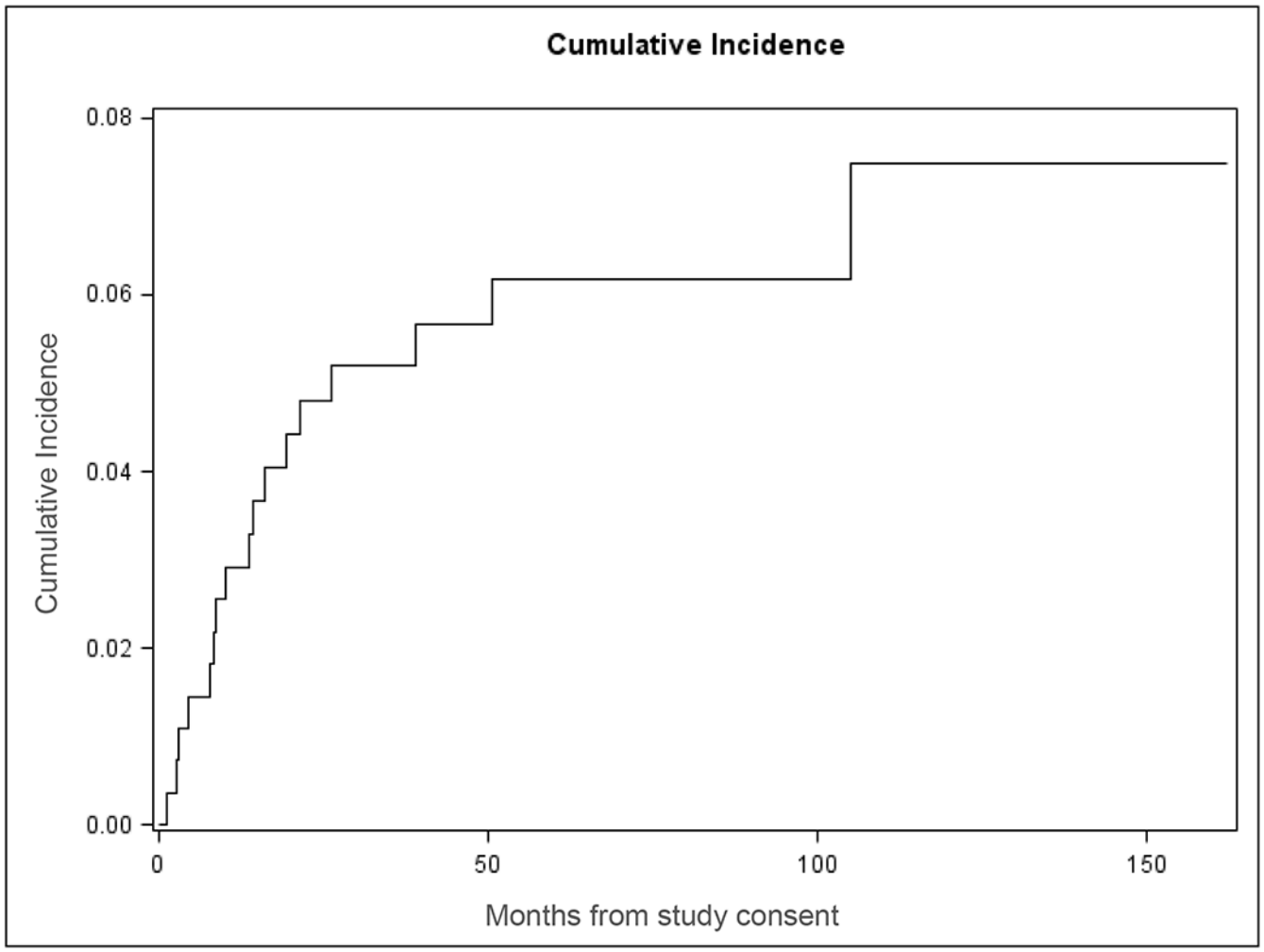

Figure 1:
Cumulative incidence of malignancy relapse.

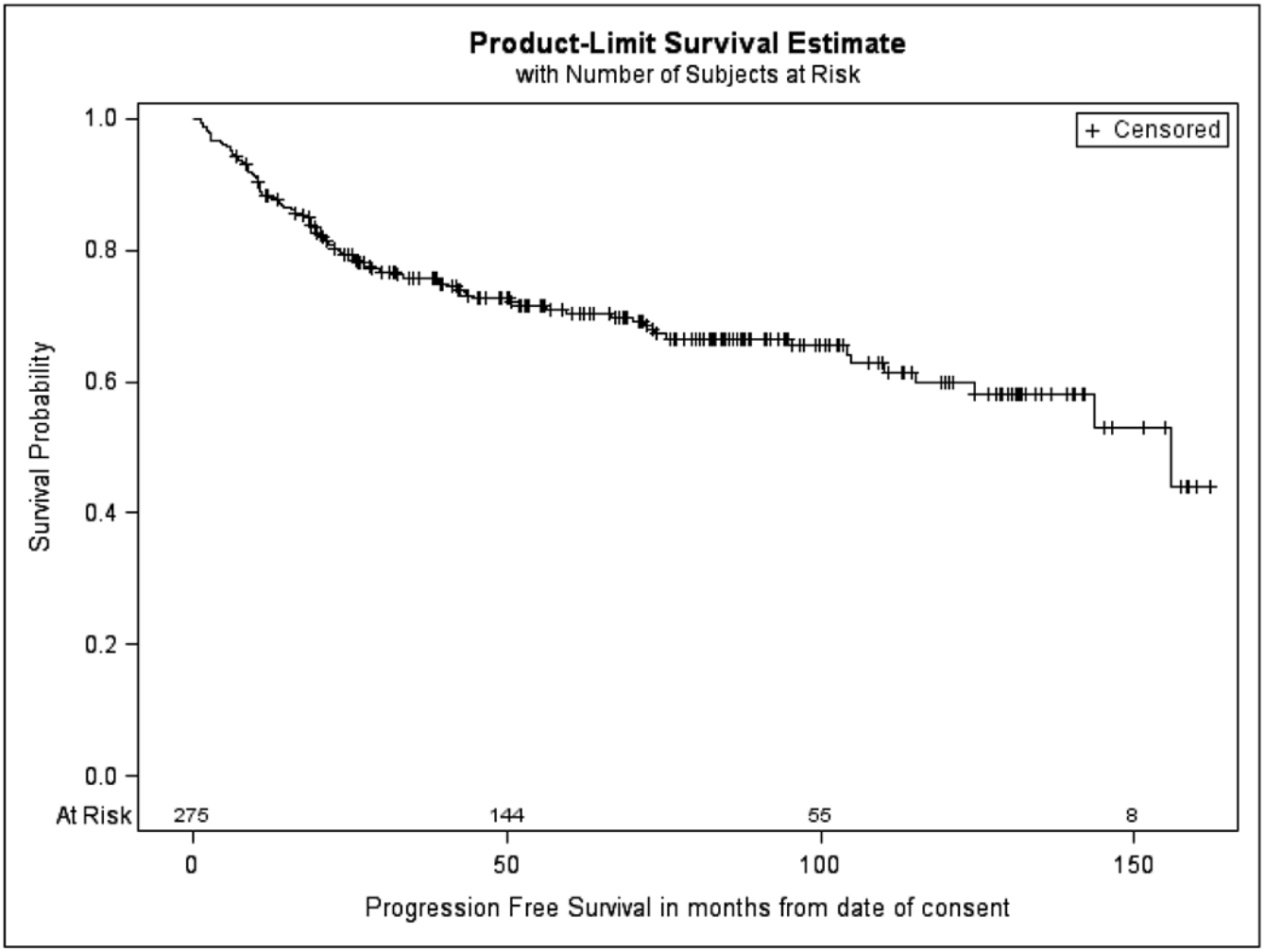

Figure 2:
Progression-free survival. Patients were censored at time of last follow-up.

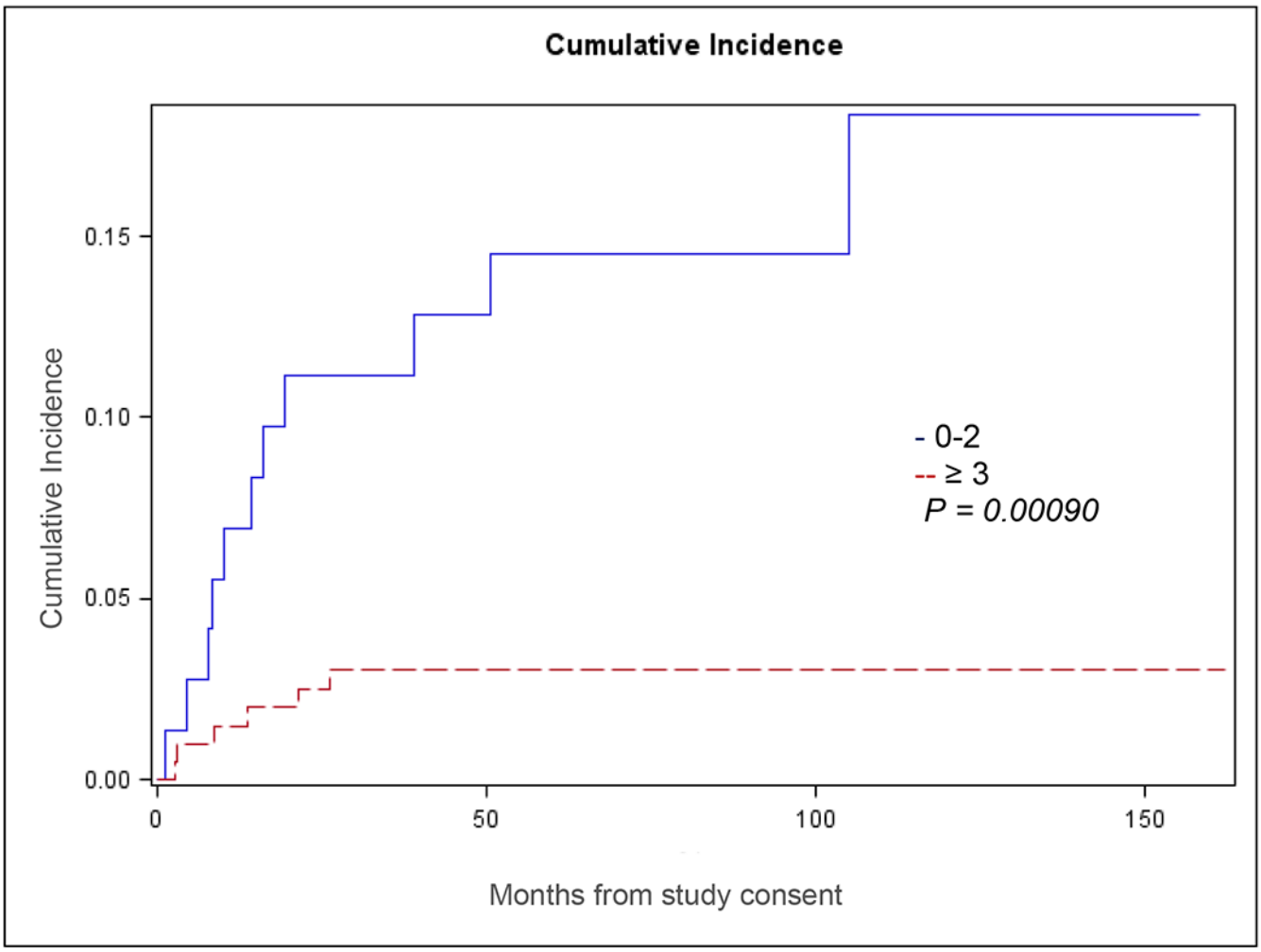

Figure 3:
Cumulative incidence of malignancy relapse by number of prior systemic treatments for chronic GVHD.

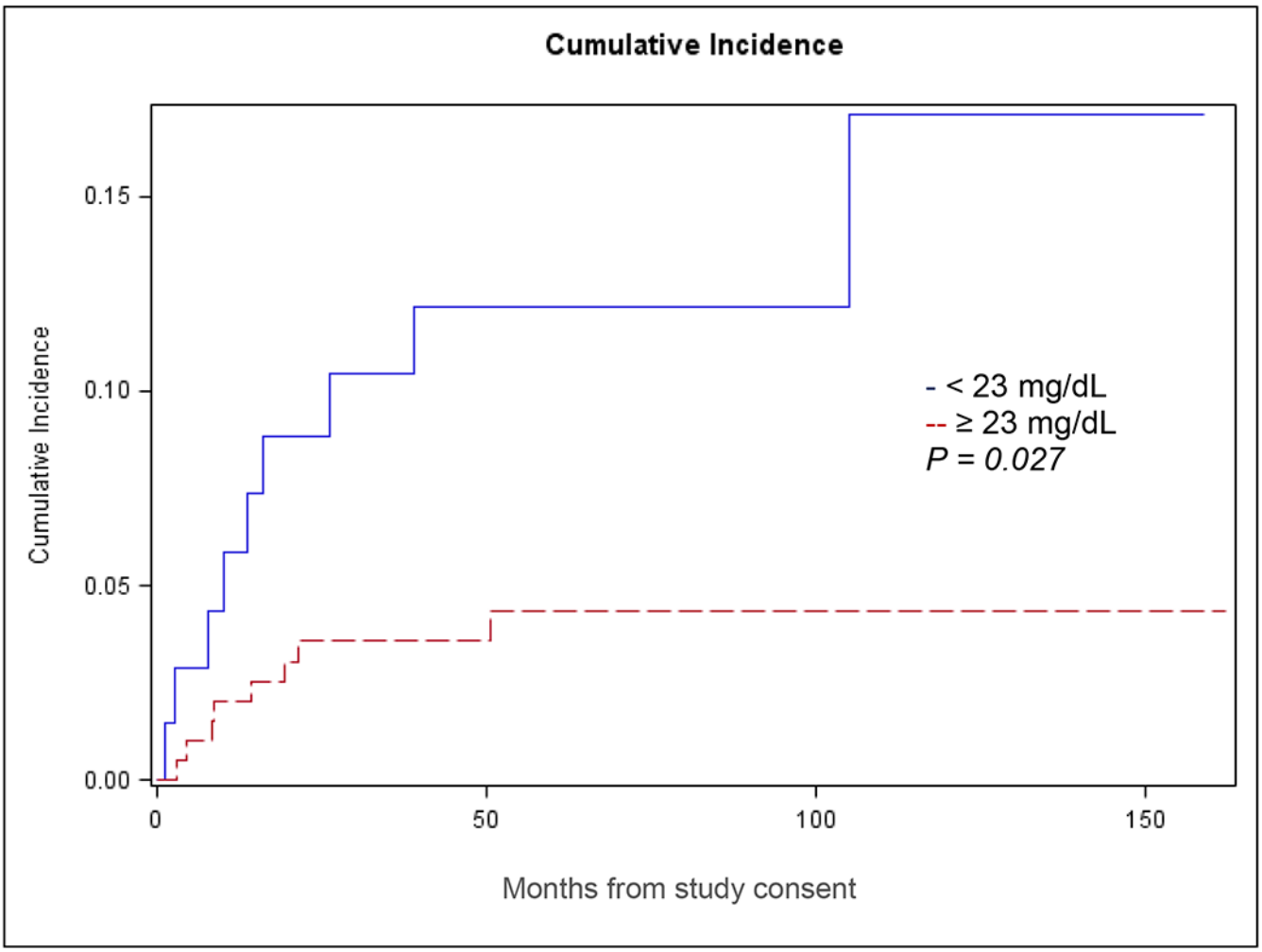

Figure 4:
Cumulative incidence of malignancy relapse by C4 complement level.

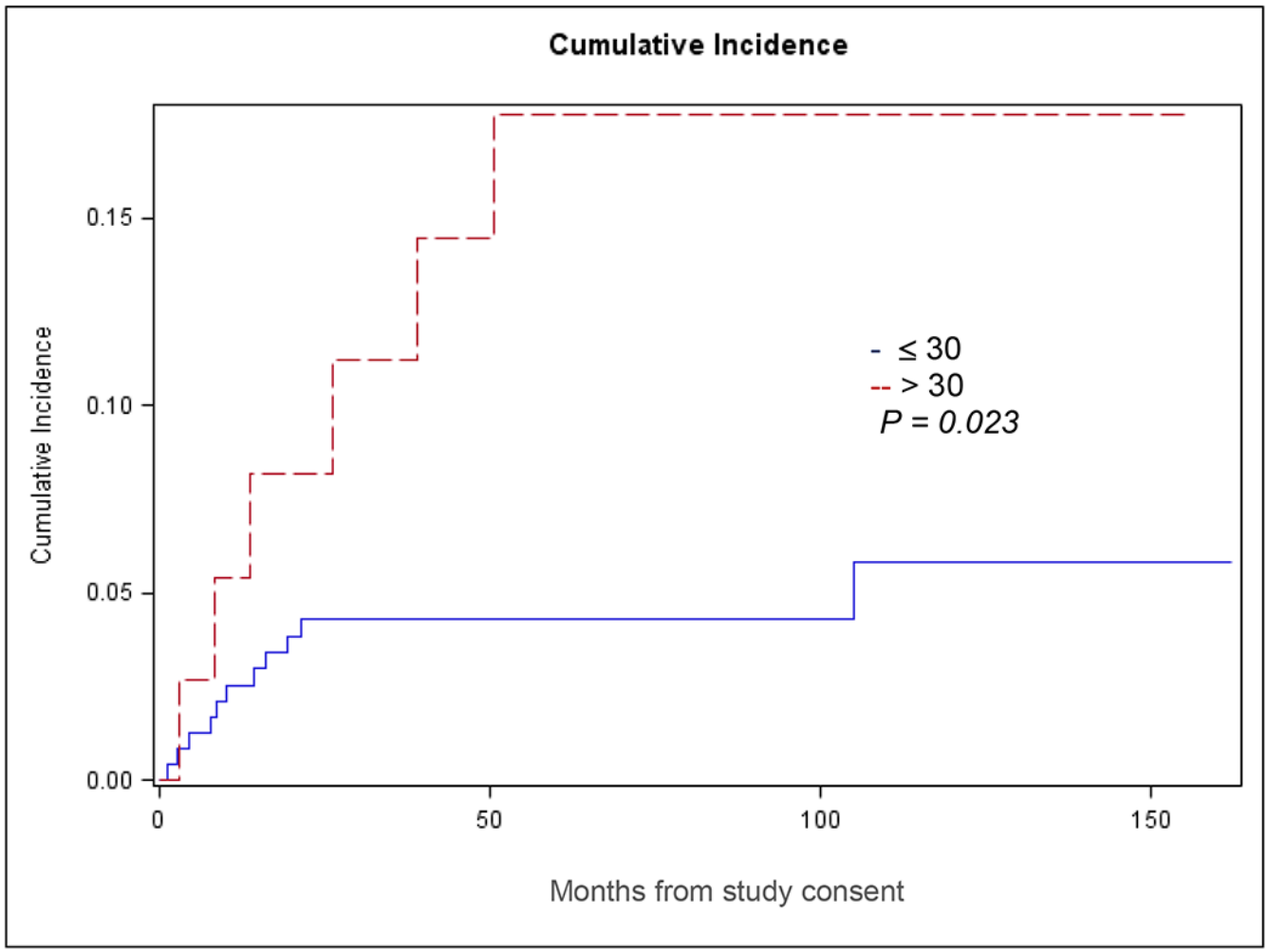

Figure 5:
Cumulative incidence of malignancy relapse by BMI.

Table 1:

Demographic characteristics of patients with chronic graft-versus-host disease.

	All Patients N (% or IQR)
All	275
Sex	
Male	152 (55)
Female	123 (45)
BMI	25 (21-28)
Age at GVHD evaluation (median)	48 (35-57)
Disease	
ALL, AML, MDS	151 (55)
CML, IMF, MPD	32 (12)
CLL	17 (6)
HL, NHL	63 (23)
MM	11 (4)
Ewing Sarcoma	1 (<1)
Disease Status at Transplant	
Complete Remission	131 (48)
Other	138 (50)
Unknown	6 (2)
Conditioning Regimen	
Myeloablative	160 (58)
Non-Myeloablative	114 (41)
Unknown	1 (<1)
Total Body Irradiation	
Yes	110 (40)
No	164 (60)
Unknown	1 (<1)
Donor Relationship	
Related	119 (43)
Unrelated	154 (56)
Unknown	2 (<1)
Stem Cell Source	
Bone Marrow	53 (19)
Peripheral Blood	216 (79)
Cord	6 (2)
T-Cell Depletion	
Yes	50 (18)
No	218 (79)

	All Patients N (% or IQR)
Unknown	7 (3)
HLA Match	
Yes	223 (81)
No	44 (16)
Unknown	8 (3)

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; CML, chronic myeloid leukemia; IMF, idiopathic myelofibrosis; MPD, myeloproliferative disorder; CLL, Chronic lymphocytic leukemia; HL, Hodgkin lymphoma; NHL, Non-Hodgkin lymphoma; MM, multiple myeloma

Table 2:

Chronic graft-versus-host disease characteristics.

	All Patients N (% or IQR)
All	275
Transplant to Consent (median, mo.)	36 (22-58)
Transplant to cGVHD Diagnosis (median, mo.)	7 (5-12)
cGVHD diagnosis to Consent (median, mo.)	24 (11-49)
cGVHD Organ Involvement	
Ocular	218 (79)
Skin	217 (79)
Lungs	203 (74)
Oral	184 (67)
Joints and Fascia	174 (63)
Liver	134 (49)
Gastrointestinal Tract	119 (43)
Genitals (females only)	67 (54)
Average NIH Organ Score	1.13 (0.75-1.43)
Number of Organs affected by cGVHD	
1-2	21 (8)
3-4	90 (33)
5-6	120 (44)
7-8	44 (16)
NIH Global Score	
Mild	6 (2)
Moderate	75 (27)
Severe	194 (71)
Prior Acute GVHD	
Yes	188 (68)
No	86 (31)
Unknown	1 (<1)
Prior cGVHD Systemic Treatment Regimens	
<2	25 (9)
2-3	93 (34)
4-5	98 (36)
>5	59 (21)
Intensity of Current Immunosuppression	
None/Mild	59 (21)
Moderate	104 (38)
High	111 (40)
Unknown	1 (<1)

NIH Global score is defined as: mild (1-2 organs affected by chronic GVHD with scores of 1), moderate (more than 2 organs with score of 1, any score of 2, or lung score of 1), or severe (any score of 3 or lung score of 2)[14]

Intensity of current immunosuppression is defined as: mild (single-agent prednisone <0.5 mg/kg/d), moderate (single-agent prednisone ≥0.5 mg/kg/d and/or any single agent/modality), high (2 or more agents/modalities +/− ≥prednisone 0.5 mg/kg/d)[15]

Table 3:

Qualitative and quantitative parameters presented according to relapse status as of date of analysis, and their association with subsequent relapse.

	Relapse (N=17) N or Median (% or IQR)	Non-Relapse (N=258) N or Median (% or IQR)	*P* *
Disease			
ALL, AML, MDS, MM, Ewing Sarcoma	11 (65)	153 (59)	0.99
CML, CLL, IMF, HL, NHL, MPD	6 (35)	105 (41)	
Time from Transplant to cGVHD diagnosis (mo)	7 (4-13)	7 (5-12)	0.36
Time from Transplant to Consent (mo)	21 (12-32)	36 (23-59)	**0.018**
Time from cGVHD Diagnosis to Consent (mo)	11 (6-19)	25 (12-51)	**0.019**
Body Mass Index			
Obese	6 (35)	31 (12)	**0.023**
Other	11 (65)	226 (88)	
Unknown	0 (0)	1 (<1)	
Total Body Irradiation			
Yes	7 (41)	103 (40)	0.97
No	10 (59)	154 (60)	
Unknown	0 (0)	1 (<1)	
Myeloablative Conditioning Regimen			
Yes	8 (47)	152 (59)	0.64
No	9 (53)	106 (41)	
Female Donor/Male Host			
Yes	3 (18)	64 (25)	0.61
No	14 (82)	188 (73)	
Unknown	0 (0)	6 (2)	
T-Cell Depletion			
Yes	2 (12)	48 (19)	0.66
No	15 (88)	203 (79)	
Unknown	0 (0)	7 (3)	
Disease Status at Transplant			
Complete Remission	5 (29)	126 (49)	0.27
Other	11 (65)	127 (49)	
Unknown	1 (6)	5 (2)	
Stem Cell Source			
Bone Marrow	2 (12)	51 (20)	0.46
Peripheral Blood	14 (82)	202 (78)	
Cord	1 (6)	5 (2)	

	Relapse (N=17) N or Median (% or IQR)	Non-Relapse (N=258) N or Median (% or IQR)	*P* *
CMV Negative Donor/CMV Negative Host			
Yes	4 (24)	60 (23)	0.94
No	13 (76)	198 (77)	
HLA Match			
Yes	15 (88)	208 (81)	0.65
No	2 (12)	42 (16)	
Unknown	0 (0)	8 (3)	
NIH GI Score			
0	14 (82)	142 (55)	
1	2 (12)	91 (35)	0.13
2	1 (6)	15 (6)	
3	0 (0)	10 (4)	
NIH Joint Score			
0	8 (47)	93 (36)	
1	6 (35)	54 (21)	0.21
2	2 (12)	78 (30)	
3	1 (6)	33 (13)	
NIH Skin Score			
0	2 (12)	56 (22)	
1	6 (35)	44 (17)	0.18
2	4 (24)	40 (16)	
3	5 (29)	118 (46)	
Global cGVHD Score			
Moderate	8 (47)	67 (26)	0.09
Severe	9 (53)	185 (72)	
Intensity of Immunosuppression			
None/Mild	7 (41)	52 (20)	
Moderate	7 (41)	97 (38)	0.058
High	3 (18)	108 (42)	
Unknown	0 (0)	1 (<1)	
Number of Prior Systemic Treatments			
0-2	11 (65)	61 (24)	**0.0009**
≥ 3	6 (35)	197 (76)	
C3 Complement	124 (100-134)	135 (120-156)	0.32
C4 Complement	20 (17-29)	28 (23-34)	**0.027**

Patients were censored at date of last follow up, thus non-relapsing patients remain at risk for relapse, and the distributions of traits shown will change as patients may relapse over time.

* P-values are the results of Gray's test for assessing the effect on relapse according to the categories shown, or the adjusted p-values after establishment of preferred groupings.

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; HL, Hodgkin lymphoma; NHL, Non-Hodgkin lymphoma; CML, chronic myeloid leukemia; CLL, chronic lymphocytic leukemia; MM, multiple myeloma; CMV, cytomegalovirus.

NIH organ scores per NIH scoring criteria (14)

Intensity of immunosuppression description and reference (15)

Table 4:

Predictive model for malignancy relapse.

	HR (95% CI)	*P*
Time from Transplant to Consent (mo)	0.279 (0.078-0.995)	0.049
Number of Prior cGVHD Systemic Treatments	0.260 (0.094-0.719)	0.0094

Table 5:

Predictive model for malignancy relapse excluding time-dependent factors.

	HR (95% CI)	*P*
Number of Prior cGVHD Systemic Treatments	0.288 (0.103-0.104)	0.0175
C4 Complement Level	0.346 (0.129-0.923)	0.0340
Body Mass Index	3.222 (1.156-8.974)	0.0252