Impact of Ocular Chronic Graft-versus-Host Disease on Quality of Life

Yi-Chen Sun, MD[1,2], **Xiaoyu Chai, MS**[3], **Yoshihiro Inamoto, MD, PhD**[3,4], **Joseph Pidala, MD**[5], **Paul J. Martin, MD**[3], **Mary E.D. Flowers, MD**[3], **Tueng T. Shen, MD, PhD**[1], **Stephanie J. Lee, MD, MPH**[3], and **Madan Jagasia, MBBS; MS**[6]

[1]Department of Ophthalmology, University of Washington, Seattle, Washington

[2]Department of Ophthalmology, Taipei Tzu Chi Hospital, The Buddhist Tzu Chi Medical Foundation

[3]Division of Clinical Research, Fred Hutchinson Cancer Research Center, Seattle, Washington

[4]Division of Hematopoietic Stem Cell Transplantation, National Cancer Center Hospital, Tokyo, Japan

[5]Department of Blood and Marrow Transplantation, H. Lee Moffitt Cancer Center, Tampa, Florida

[6]Division of Hematology/Oncology, Stem Cell Transplantation, Department of Medicine, Vanderbilt University, Nashville, Tennessee

Abstract

Ocular involvement can be quite symptomatic in patients with chronic graft-versus-host disease (GVHD). The prevalence of and risk factors for ocular GVHD and its impact on quality of life (QOL) in patients with chronic GVHD were studied in a prospective, multicenter, longitudinal, observational study. This study enrolled 342 patients with 1,483 follow-up visits after allogeneic hematopoietic cell transplantation. All patients in this analysis were diagnosed with chronic GVHD requiring systemic treatment and enrolled within 3 months of chronic GVHD diagnosis. The symptom burden of ocular GVHD was based on the degree of dry eye symptoms, frequency of artificial tear usage, and impact on activities of daily living. Patients' quality of life (QOL) was measured by self-administered questionnaires. Variables associated with ocular GVHD at enrollment and subsequent new onset ocular GVHD, and the associations with QOL were studied. Of the 284 chronic GVHD patients, 116 (41%) had ocular GVHD within 3 months of chronic GVHD diagnosis ("early ocular GVHD"). Late ocular GVHD (new onset > 3 months after chronic GVHD diagnosis) occurred in 64 patients. Overall cumulative incidence at 2 years was 57%. Female gender (p=0.005), higher acute GVHD grade (p=0.04) and higher prednisone dose at study entry (p=0.04) were associated with early ocular GVHD. For patients who did not have ocular GVHD within 3 months of chronic GVHD diagnosis, presence of prior grade I-IV acute GVHD

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(HR 1.78, P=0.04) was associated with shorter time to late ocular GVHD, while female donor into male recipient (HR 0.53, P=0.05) was associated with longer time to late ocular GVHD onset. Utilizing all visit data, patients with ocular GVHD had worse quality of life as measured by FACT-BMT (P=0.002), and greater chronic GVHD symptom burden, as measured by the Lee symptom overall score excluding the eye component (P<0.001) compared to patients who did not have ocular GVHD. In conclusion, this large multicenter, prospective study shows that ocular GVHD affects 57% of patients within 2 year of chronic GVHD diagnosis. Women, patients on higher doses of prednisone at study entry, and those with a history of acute GVHD were at higher risk for ocular GVHD. Strong evidence suggests that ocular GVHD is associated with worse overall health-related QOL.

Introduction

Since the first successful bone marrow transplantation in 1968, allogeneic hematopoietic cell transplantation (HCT) is used with increasing frequency for treatment of hematological disorders (both malignant and non-malignant) with curative intent.[1,2] Graft-versus-host disease (GVHD) caused by alloreactive donor T cells remains an important cause of non-relapse mortality and morbidity after allo-HCT.[3] Chronic GVHD typically starts more than 3 months after transplant, and may persist for many years. Chronic GVHD most often involves the mouth and skin, but it can also affect multiple sites, such as eyes, gastrointestinal tract, liver, lungs, and genital tract.[4,5]

Ocular GVHD reportedly occurs in more than 50% of allogeneic HCT recipients with chronic GVHD.[5] The most frequent ocular symptoms are a sensation of dryness, irritation, redness, and photophobia. Ocular GVHD can affect all parts of the eye, but the ocular surface is the most common level of involvement.[6–8] Conjunctival involvement has been associated with higher mortality[9] and worse quality of life[10] in prior single-centered and small-grouped reports.

Quality of Life (QOL) is defined as the general well-being of individuals and societies.[11] It is a multidimensional concept, and health is one of the important dimensions of overall quality of life. The QOL in patients with ocular disorders can be affected by ocular symptoms, such as blurred vision, severe photophobia, or having difficulties in keeping eyes open due to discomfort.[12–14] Affected patients might not be able to drive, read, watch television, or perform other common activities in their routine daily life. In this study we describe the epidemiology of ocular GVHD symptoms in patients with chronic GVHD, perform a risk factor analyses, and describe the impact of ocular involvement on QOL.

Materials and Methods

Data were derived from the Chronic GVHD Consortium, a multicenter observational cohort study of chronic GVHD-affected HCT recipients. The rationale and design of this cohort study have been previously described.[16] Patients with chronic GVHD requiring systemic treatment were enrolled if the time from onset of GVHD was 2 years or less. Cases were defined as incident if onset of chronic GVHD was within 3 months of study enrollment and prevalent if onset of chronic GVHD was > 3 months of study enrollment. For this analysis,

only incident cases were included. The study protocol was approved by the institutional review board of each participating center, and all participants or their guardians gave written informed consent. Patients had detailed assessment by the transplant clinician or trained provider at pre-specified time-points as required by the protocol using a variety of assessment tools.[16] Scoring of chronic GVHD was done using the NIH Consensus Criteria.[15] Ocular involvement is scored on a 0–3 scale and is dependent on the degree of dry eye symptoms, frequency of eye drops or intervention for dry eye, and impact on activities of daily living.[17] Patients completed detailed QOL questionnaires, including the Functional Assessment of Cancer Therapy Bone Marrow Transplantation (FACT-BMT)[18,19] the Short Form (36) Health Survey, which provides a Physical Component Score (SF36 PCS) and Mental Component Score (SF36 MCS);[20,21] the Human Activity Profile providing a Maximum Activity Score (HAP MAS),[22] Adjusted Activity Score (HAP AAS), and modified HAP AAS[23]; and the Lee symptom score[24] at these visits. The QOL metrics were not designed specifically for ocular disorders but measure a person's multi-dimensional QOL.

Definition

For this study, the ocular GVHD group was defined as eye involvement reported by both the clinician (NIH 0–3 eye score > 0) and patient (eye worst 0–10 score > 1 or Lee symptom eye score > 20)[25]. It is likely that risk factors associated with ocular GVHD may vary depending on time of onset of ocular GVHD in relation to development of systemic chronic GVHD. Thus, early ocular GVHD was defined as the onset of ocular involvement at study enrollment and late ocular GVHD was defined as onset three or more months after the diagnosis of chronic GVHD. Ocular assessments prior to HCT or prior to study enrollment were not routinely performed.

Statistical analysis

Descriptive statistics, including continuous variables and categorical variables, were calculated and reported in Table 1 and Table 2. All the variables we analyzed were as below: age at HCT, patient gender, donor and patient gender combination, preparative regimen intensity, donor match status, source of stem cells, prior acute GVHD, maximum acute GVHD grade (overall, liver, gastrointestinal, and skin), underlying diseases, disease status, platelet count at onset and enrollment, bilirubin level at onset and enrollment, prednisolone dose at onset and enrollment, worst Schirmer's test at enrollment, study site (FHCRC vs. others), and duration from treatment to enrollment. Univariable and multivariable logistic regression models were fit to identify risk factors that were associated with ocular GVHD at enrollment. To identify the risk factors that are associated with development of ocular GVHD at subsequent follow up, Cox regressions were fit for patients who did not have ocular GVHD at enrollment (N=168). Relapse and death before the onset of ocular GVHD were treated as competing events. Cox regressions were also fit for overall survival (OS) and nonrelapse mortality (NRM) of the two cohorts (chronic GVHD with and without ocular GVHD at study enrollment). Covariates significantly associated with outcomes were included for adjustment, including platelet count (<100,000/μl or >=100,000/μl), donor gender combination (female into male or others), bilirubin (2 mg/dL or higher), and NIH global severity (mild or less, moderate, or severe). Linear mixed models with random patient

effect were fit for evaluating the ocular involvement associated with QOL, including functional and symptom measures, adjusted for significant clinical covariates. The covariates included study site (FHCRC or others), months since enrollment, platelet count (<100,000/μl or >=100,000/μl), NIH global severity (mild or less, moderate, or severe), bilirubin (2 mg/dL or higher), overlap or classic, and prior acute GVHD. A *p*-value below 0.05 was considered statistically significant.

Statistical analyses were performed using SAS/STAT software, version 9.4 (SAS Institute, Inc., Cary, NC) and R version 3.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

General characteristics of the patients included in this study are presented in Table 1. This study included 342 adult patients who had 1,483 visits. The median follow-up time was 28 months from enrollment in the study (range 4–66 months). The cumulative incidence of all ocular GVHD at 2 years after enrollment was 57% (95% CI 52%–63%). The incidence of ocular GVHD between FHCRC and other centers was also analyzed and no significance was noted (*p* value = 0.49).

Risk factor analysis of early ocular GVHD

Of the 342 patients, 284 (83%) patients had complete clinician and patient-reported ocular data at study enrollment. Of the 284 patients, 116 (41%) had ocular GVHD confirmed by both clinician and patient-report within 3 months of chronic GVHD diagnosis ("early ocular GVHD") (Table 2). Most of the early ocular GVHD patients (71%) had mild ocular symptoms (NIH eye score: 1). Among the 116 early ocular GVHD patients, Schirmer's test was measured in 89 patients (77%), of which 59 patients (66%) had a mean value of 10 mm or less. In a multivariable analysis, female sex (odds ratio [OR]=2.14, 95% CI 1.26–3.63 *P*=0.005), overall maximum acute grade (OR=1.32, 95% CI 1.01–1.73 *P*=0.04) and higher prednisone dose at study entry (OR=2.04, 95% CI 1.04–4.00, *P*=0.04) were associated with early ocular GVHD (Table 3).

Development and risk factor analysis of late ocular GVHD

Late ocular GVHD (new onset after study enrollment) occurred in 64 patients who were confirmed not to have ocular GVHD at enrollment. The cumulative incidence of late ocular GVHD at 2-year post enrollment was 37% (95% CI 30%–46%) (Figure 1). In multivariable modeling, presence of prior grade I-IV acute GVHD (HR 1.78, *P*=0.04) was associated with shorter time to late ocular GVHD, while female donor into male recipient (HR 0.53, *P*=0.05) was associated with longer time to late onset ocular GVHD (Table 4).

Eighteen of the 58 patients (31%) whose ocular GVHD could not be classified at enrollment because of missing clinician or patient information subsequently had confirmed ocular GVHD later in their course. These patients were excluded from the analysis of late ocular GVHD predictors since we are uncertain if they had early or late onset ocular GVHD.

Survival and non-relapse mortality

In multivariate Cox models with ocular GVHD as a time-varying covariate, ocular GVHD was not associated with survival (HR 1.08, P=0.76) or subsequent non-relapse mortality (HR 1.27, P=0.48)

Analysis between quality of life and ocular GVHD

Table 5 shows the association of ocular GVHD with patient-reported QOL, using all available visit data adjusted for center effect, months since enrollment, platelet count, NIH severity, bilirubin, prior acute GVHD, and overlap vs. classic chronic GVHD. The association between QOL and ocular involvement is significant, especially in the FACTBMT score (P<0.01) despite adjusting for the clinical factors. The Lee symptom score overall (excluding the eye component to avoid bias from eye symptoms) is also highly associated with ocular involvement (P <0.001). The other QOL questionnaires, including SF36 and HAP, did not show significant association with ocular involvement (P >0.05).

Discussion

This study describes the high incidence of symptomatic ocular GVHD in patients with established chronic GVHD in a longitudinal prospective cohort. In our cohort, 41% of patients had ocular GVHD symptoms within 3 months after diagnosis of chronic GVHD and another 23% developed ocular GVHD by 2 years after chronic GVHD onset for a 2-year cumulative incidence of 57%. Thus, patients with chronic GVHD who do not have ocular GVHD at onset of chronic GVHD remain at significant risk of subsequently developing eye symptoms later and should be carefully monitored.

Some study limitations should be noted. We categorized ocular GVHD according to the tools recommended by the 2005 NIH Consensus Conference on Criteria for Clinical Trials in Chronic GVHD. These assessments were designed so they could be collected from transplant providers and patients, and not require subspecialists.[15,28] Indeed, many of the patients in our study were managed by their transplant physicians and not by ophthalmologists. Although, Schirmer's test was performed in the majority of the patients, results are not used in severity scoring, as it is known to be unreliable.[25–27] The change in light, humidity and temperature and patient anxiety may interfere with the tear reflex.[26] The paper's contact with eyelashes and the position of the paper placed on the lid margin are also the factors which can explain the large discrepancies in the reported repeatability of the Schirmer's test.[27] We acknowledge that other etiologies besides ocular GVHD could contribute to dry eye symptoms in our population and could confound the analyses. A comprehensive assessment by ophthalmologists would provide more detailed, and likely more accurate, information about ocular involvement, but referral is not uniformly practiced. In addition, multiple consensus criteria for severity scoring have been proposed by the ophthalmology community but none have been validated, suggesting that while the evaluation may be more complete, the ability to use that information to quantify the severity of involvement is not robust yet.[17] A recent analysis compared the Japanese dry eye score and the Dry Eye Workshop Score (DEWS) to the NIH eye score,[28] and found excellent correlation among the 3 scoring systems, lending support to the accuracy of transplant

physicians' in assessing severity. However, a prospective study using ophthalmology examinations as the gold standard is still necessary and important for further evaluation of ocular GVHD.

Risk factors for ocular GVHD have been reported in retrospective studies. In addition to global GVHD, prior acute skin GVHD and male recipients of female donors were reported as two independent risk factors for ocular GVHD.[29] A higher incidence of ocular GVHD after peripheral blood stem cell transplantation than bone marrow transplantation (BMT) or cord blood transplantation was reported by Uchino M, et al. in 2012.[30] In our prospective study, independent risk factors for early ocular GVHD included female sex, more severe acute GVHD, and higher prednisone dose at enrollment. Female predilection for early ocular GVHD in this study (median age 51 years old) is compatible with the predisposing factors for dry eye syndrome, such as middle age and female gender.[31] The biological reasons for these associations remain unknown, but may involve common pathways. Interestingly, it seems that acute GVHD could predict development of early ocular GVHD as well as late ocular GVHD. In multivariable modeling, presence of prior grade I-IV acute GVHD was associated with shorter time to late ocular GVHD, while female donor into male recipient was associated with longer time to late ocular GVHD onset. These results should help define risk stratification of patients in future clinical trials addressing prevention of ocular GVHD.

Quality of life measures capture the impact of medical conditions on physical, social, emotional, cognitive, work- or role-related, and spiritual aspects of life. GVHD has consistently been shown to have a major impact on patients' quality of life. Lee et al.[32] showed that both grades II-IV acute and chronic GVHD were associated with worse QOL after HCT. Pallua and colleagues[33] also found that patients suffering from chronic GVHD showed worse role functioning and global QOL, and had a higher likelihood of taking chronic medications. Pidala et al.[34] reported that chronic GVHD severity defined by NIH criteria was independently associated with QOL. Riemens et al.[10] used two questionnaires (VFQ-25: visual function questionnaire-25 and OSDI: ocular surface disease index) to assess vision-related QOL in 2014. Their results showed that patients who developed ocular GVHD (N=14) have impaired visual QOL.

In this study, we focused on the relationship between ocular GVHD and health-related QOL instead of vision-related QOL, to study the impact of dry eye symptoms on general QOL. Several different questionnaires, including FACT-BMT, SF36, HAP, and Lee symptom score were used to assess the QOL of ocular GVHD patients. FACT-BMT is an outcome measure for health-related quality of life. SF-36 is a measure more about general health and HAP is for functional performance and activity limitation in adults. We found that FACT-BMT and Lee symptom score (without the eye subscale) showed significant differences between patients with and without ocular GVHD symptoms, adjusting for other clinical factors. The association of ocular GVHD and FACT-BMT and no association with SF-36 and HAP might be because of the characteristic of ocular GVHD which is an ocular surface disorder causing a lot of eye discomforts but not necessarily affecting vision to impact activity and functional performance. To our knowledge, this is the first prospective study investigating the association of ocular GVHD and health-related QOL. There was no correlation with SF36 and HAP.

In conclusion, we found that the patients with more severe acute GVHD developed ocular GVHD coincident with their diagnosis of chronic GVHD and remained at higher risk for subsequent late onset ocular GVHD. Approximately a third of patients with chronic GVHD had ocular GVHD at diagnosis, while almost a quarter developed ocular GVHD at later time points. A significant relationship between ocular GVHD and non-vision related QOL and non-ocular GVHD symptoms was also revealed in this study. Ocular GVHD may cause permanent destruction of lacrimal glands, resulting from increase in number of stromal fibroblasts and excessive fibrosis in the extracellular matrix of the lacrimal glands.[35] Early initiation of topical cyclosporine-A 0.05% in ocular GVHD patients could relieve the patients' dry eye symptoms as well as might reduce the inflammatory response in the lacrimal glands.[36] Ideally, prophylactic or pre-emptive clinical trial (NCT00755040, pending analyses) strategies prior to onset of irreversible dry eye syndrome are needed. Comprehensive ophthalmologic assessment should be undertaken in patients at high risk for ocular GVHD, and in patients with ocular symptoms. Preventive evaluation at set time-points after transplant to screen of asymptomatic ocular GVHD is encouraged.

Acknowledgments

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Highlights

- We report aA prospective, multicenter study correlating about the impact of ocular GVHD on quality of life.

- The risk factors of early developing ocular GVHD are female gender, more severe prior acute GVHD, and higher prednisone dose at enrollment.

- Early referral to an ophthalmologist for high-risk patients is highly recommended for the prevention of permanent damage by ocular GVHD.
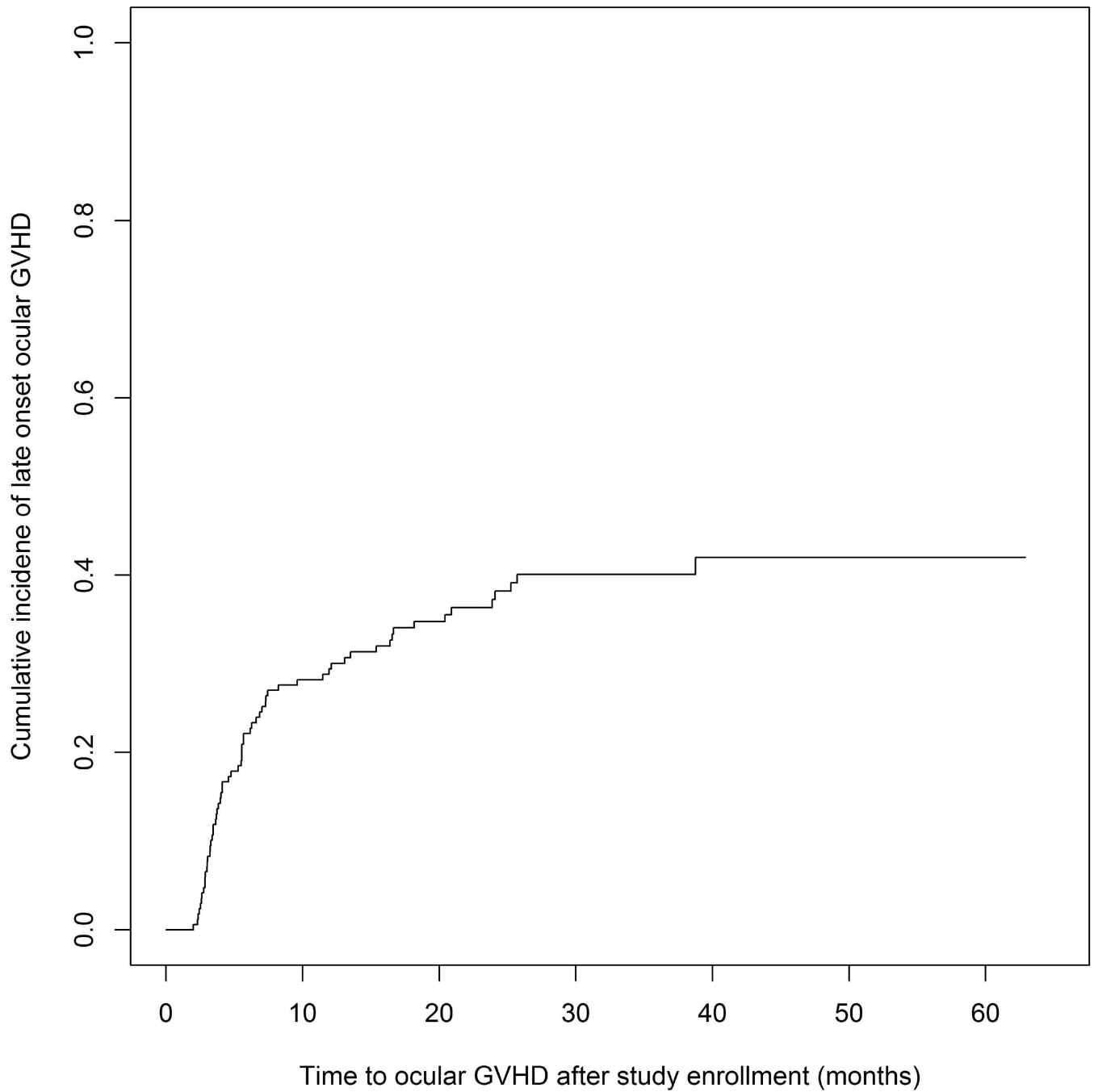
Figure.
Cumulative incidence of subsequent late ocular GVHD[*] among patient without ocular GVHD at study enrollment (N=64) ([*]late ocular GVHD: ocular GVHD onset > 3 months after diagnosis of chronic GVHD)

Table 1

Patient characteristics at study enrollment (N=342)

Variable	N (%)
Age (years), median (range)	51 (19–79)
Recipient gender	
Male	190 (56%)
Female	152 (44%)
Male recipient/female donor	92 (27%)
Transplant type	
Myeloablative	196 (58%)
Non-myeloablative	143 (42%)
Donor status	
Matched related	145 (43%)
Matched unrelated	142 (42%)
Mismatched	53 (15%)
Prior acute GVHD	
Yes	224 (66%)
No	118 (34%)
Ocular GVHD	
Yes	116 (34%)
No	168 (49%)
Unclassifiable at enrollment (Missing either clinician or patient information)	58 (17%)

Table 2

Ocular characteristics of early ocular GVHD[*] patients (N=116)

Variable	N (%)
National Institute of Health (NIH) eye score	
0	0 (0%)
1	82 (71%)
2	32 (27%)
3	2 (2%)
Schirmer's test (worst eye)	
>10 mm	30 (26%)
5–10 mm	29 (25%)
<5 mm	30 (26%)
Missing	27 (23%)

[*] early ocular GVHD: ocular GVHD onset within 3 months after diagnosis of cGVHD

Table 3

Multivariable analysis of risk factors associated with early ocular GVHD[*] involvement in chronic GVHD patients at enrollment (N=116)

Covariate	Effect	Odds ratio	95% CI	P-value
Patient gender	Female vs. Male	2.14	1.26–3.63	0.005
Max acute GVHD grade: overall	Continuous 0–4	1.32	1.01–1.73	0.04
Prednisone dose at enrollment	Continuous	2.04	1.04–4.00	0.04

[*] early ocular GVHD: ocular GVHD onset within 3 months after diagnosis of chronic GVHD

Table 4

Multivariable analysis of risk factors associated with late ocular GVHD[*] involvement (N=168, Number of events=64)

Covariate	Effect	HR	95% CI	P-value
Prior grade I–IV acute GVHD	Yes vs. No	1.78	1.04–3.20	0.04
Donor/patient gender combination	Female into male vs. Others	0.53	0.27–0.96	0.05

[*] late ocular GVHD: ocular GVHD onset > 3 months after diagnosis of chronic GVHD

Table 5

The association between quality of life (QOL) and ocular GVHD in chronic GVHD patients

QOL Metric	Ocular GVHD	Estimate	P
	No	0[*]	
FACT-BMT	Yes	−3.0	0.002
	No	0[*]	
Lee Score[**]	Yes	2.9	<0.001

[*] Estimate 0-reference category;

[**] Lee symptom score-eye component excluded