Biol Blood Marrow Transplant 21 (2015) 1687–1691

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

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

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

[1] Department of Ophthalmology, University of Washington, Seattle, Washington
[2] Department of Ophthalmology, Taipei Tzu Chi Hospital, The Buddhist Tzu Chi Medical Foundation, New Taipei City, Taiwan
[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

Article history:
Received 3 April 2015
Accepted 22 May 2015

Key Words:
Ocular graft-versus-host disease
Quality of life
Risk factors

A B S T R A C T

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 1483 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' 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 ($P = .005$), higher acute GVHD grade ($P = .04$), and higher prednisone dose at study entry ($P = .04$) were associated with early ocular GVHD. For patients who did not have ocular GVHD within 3 months of chronic GVHD diagnosis, presence of prior grades I to IV acute GVHD (HR 1.78, $P = .04$) was associated with shorter time to late ocular GVHD, whereas female donor–male recipient (HR .53, $P = .05$) was associated with longer time to late ocular GVHD onset. Using all visit data, patients with ocular GVHD had worse QOL, as measured by Functional Assessment of Cancer Therapy Bone Marrow Transplantation ($P = .002$), and greater chronic GVHD symptom burden, as measured by the Lee symptom overall score excluding the eye component ($P < .001$), compared with patients without ocular GVHD. In conclusion, this large, multicenter, prospective study shows that ocular GVHD affects 57% of patients within 2 years 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 nonmalignant) with curative intent [1,2]. Graft-versus-host disease (GVHD) caused by alloreactive donor T cells remains an important cause of nonrelapse mortality and morbidity after allogeneic 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 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,

Financial disclosure: See Acknowledgments on page 1690.

* Correspondence and reprint requests: Dr. Madan Jagasia, Department of Medicine, Division of Hematology/Oncology, Stem Cell Transplantation, Vanderbilt University, 3973 TVC, 2220 Pierce Ave, 777 PRB, Nashville, TN 37232.
E-mail address: madan.jagasia@vanderbilt.edu (M. Jagasia).

http://dx.doi.org/10.1016/j.bbmt.2015.05.020
1083-8791/

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 (QOL) [10] in prior single-centered and small-grouped reports.

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 QOL. The QOL in patients with ocular disorders can be affected by ocular symptoms, such as blurred vision, severe photophobia, or discomfort that makes it uncomfortable to keep eyes open [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 analysis, and describe the impact of ocular involvement on QOL.

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 [15] . 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 assessments by the transplant clinician or trained provider at prespecified time points as required by the protocol using a variety of assessment tools [15]. Scoring of chronic GVHD was done using the National Institutes of Health (NIH) consensus criteria [16]. Ocular involvement was scored on a scale from 0 to 3 and depended on the degree of dry eye symptoms, frequency of eye drops or intervention for dry eye, and impact on activities of daily living [17]. At these visits, patients completed detailed QOL questionnaires, including the Functional Assessment of Cancer Therapy Bone Marrow Transplantation (FACT-BMT) [18,19]; the Short Form 36 (SF-36) Health Survey, which provides a Physical Component Score and Mental Component Score [20,21]; the Human Activity Profile (HAP), providing a Maximum Activity Score [22], Adjusted Activity Score, and modified HAP Adjusted Activity Score [23]; and the Lee symptom score [24]. The QOL metrics were not designed specifically for ocular disorders but measure a person's multidimensional QOL.

Definitions

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 3 or more months after the diagnosis of chronic GVHD. Ocular assessments before HCT or before study enrollment were not routinely performed.

Statistical Analysis

Descriptive statistics, including continuous variables and categorical variables, were calculated and are reported in Tables 1 and 2. Variables analyzed were 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 (Fred Hutchinson Cancer Research Center [FHCRC] versus 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 risk factors associated with the 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 and nonrelapse mortality of the 2 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–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. $P < .05$ 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).

Table 1
Patient Characteristics at Study Enrollment (N = 342)

Variable	No. of Cases (%)
Age, yr, median (range)	51 (19-79)
Recipient gender	
Male	190 (56%)
Female	152 (44)
Male recipient–female donor	92 (27)
Transplant type	
Myeloablative	196 (58)
Nonmyeloablative	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)

RESULTS

General characteristics of the patients included in this study are presented in Table 1. This study included 342 adult patients who had 1483 visits. The median follow-up time was 28 months from enrollment in the study (range, 4 to 66). The cumulative incidence of all ocular GVHD at 2 years after enrollment was 57% (95% confidence interval [CI], 52% to 63%). The incidence of ocular GVHD between FHCRC and other centers was also analyzed, and no significance was noted ($P = .49$).

Table 2
Ocular Characteristics of Early Ocular GVHD* Patients (n = 116)

Variable	No. of Cases (%)
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 chronic GVHD.