Chronic Ocular Surface Disease after Allogeneic Bone Marrow Transplantation

MINI BALARAM, MD,[1,2] SAADIA RASHID, MD,[2,3] AND REZA DANA, MD, MSC, MPH[1,2,3]

ABSTRACT **Graft-versus-host disease (GVHD) is a common complication of allogeneic bone marrow transplantation (allo-BMT). Ocular surface disease (OSD) is one of the most common manifestations of chronic ocular GVHD, yet little is known about it. In this article, we review the available literature on this condition and present results from our study of the manifestations of OSD in the chronic phase (>3 months duration) post allo-BMT. Our study consisted of a retrospective chart review of 62 allo-BMT patients with chronic OSD evaluated at our center between 1995 and 2002. The clinical features, systemic associations, treatment, and status of OSD at the last follow-up are presented and discussed in the context of other reports of OSD in GVHD.**

KEY WORDS **allogeneic bone marrow transplantation, graft-versus-host disease, ocular surface disease**

I. INTRODUCTION

Allogeneic bone marrow transplantation (**allo-BMT**) has gained widespread acceptance as an effective therapy for many hematologic diseases and some nonhematologic malignancies.[1,2] However, allo-BMT is not without complications, despite significant advances in immunosuppressive strategies and prophylaxis against opportunistic infections.[2-5] Graft-versus-host disease (**GVHD**) continues to be the main cause of morbidity and death in well-engrafted BMT recipients.[5] Ocular complications are very common post allo-BMT,[5-12] particularly involving the anterior segment.[8-15] These include dry eye syndrome and keratoconjunctival inflammation due to GVHD, and cataract formation. Ocular surface disease (**OSD**), due to GVHD-induced lacrimal insufficiency and mucosal inflammation, can result in considerable morbidity and negatively impact the quality of life in these patients.[5,11-15] In its severest forms, ocular GVHD may be vision-threatening, and it is often difficult to treat.[6-9]

While it has been suggested that ocular complications may develop in up to 90% of long-term survivors of BMT,[7] most of the current knowledge on the subject is derived from the study of *acute* ocular disease (first 90 days) post-BMT.[6,16] In addition, the majority of data regarding therapy of ocular surface complications post-BMT or hematopoietic stem cell transplantation (**HSCT**) are derived from small case series.[16-20] Indeed, little is known about the natural history of the disease or the efficacy of currently used therapies for the treatment of chronic OSD in allo-BMT patients. We have retrospectively evaluated data from the charts of 62 patients, the largest cohort studied so far of chronic GVHD patients with OSD. In this article, we review the published literature on this condition and contribute new information from our study.

II. THE CURRENT STUDY

A. Methods

Chart review was performed for all (N=114) allo-BMT recipients who had ocular examinations at the Massachusetts Eye and Ear Infirmary/Brigham and Women's Hospital during the period January 1995-June 2002. The data recorded included the indication for BMT, type of donor (related or unrelated), human leukocyte antigen (**HLA**) match, total body irradiation (**TBI**) as pre-BMT conditioning, GVHD prophylaxis, the occurrence of acute GVHD (within 3 months of BMT) or chronic GVHD (>3 months post-BMT), and the therapeutic interventions. The research followed the tenets of the Declaration of Helsinki and was approved by Partners Human Studies Committee, the Institutional Review Board.

Inclusion criteria were two or more comprehensive oph-

Accepted for publication August 2005.

From the[1]Department of Ophthalmology, Massachusetts Eye and Ear Infirmary and Brigham and Women's Hospital, [2]Harvard Medical School, and [3]Schepens Eye Research Institute, Boston, Massachusetts, USA

The authors have no proprietary interest in any concept or product discussed in this article.

Single copy reprint requests to Reza Dana, MD, MSc, MPH (address below).

Corresponding Author: Reza Dana, MD, MSc, MPH, Schepens Eye Research Institute, 20 Staniford Street, Boston MA 02114. Tel: 617-912-7404. Fax: 617-912-0117. E-mail: dana@vision.eri.harvard.edu

Abbreviations are printed in **boldface** where they first appear with their definitions.

 The Ocular Surface ISSN: 1542-0124. Balaram M, Rashid S, Dana R. Chronic ocular surface disease after allogeneic bone marrow transplantation. 2005;3(4):203-210.

ARTICLE OUTLINE

thalmic examinations at the Cornea and Ocular Immunology Clinics, including determination of best-corrected visual acuity, slit-lamp examination, vital dye staining of the ocular surface, tear break-up time (**TBUT**) measurement, Schirmer I testing (with topical anesthesia), applanation tonometry, and dilated funduscopic examination. We required two visits, because we considered one visit inadequate to definitely identify patients with chronic OSD manifestations. Because of the retrospective nature of the study, it was not possible to obtain antecedent patient histories.

There is no unanimously accepted definition of chronic "conjunctival" GVHD. In this study, we describe the range of ocular surface (including corneal and conjunctival) changes that accompany GVHD.

We defined *chronic* post-BMT OSD as the presence of two or more of the following signs[21,22] documented in at least one examination 3 or more months post allo-BMT in a patient who had subjective symptoms of dry eye: tear film instability (TBUT ≤ 5 seconds), lacrimal insufficiency (Schirmer I test score of ≤ 5mm/5 minutes), and ocular surface abnormality indicated by vital dye staining grades 1 or higher. The grading scheme was adapted from the Report of the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eye.[21,23] We further defined chronic OSD as *mild* (vital dye staining score 1-5 with TBUT =5 seconds and/ or Schirmer I test score ≤ 5mm/5 minutes), *moderate* (vital dye staining score 6-10 with TBUT ≤ 5 seconds and/ or Schirmer I test score of ≤ 5mm/5 minutes) or *severe* (vital dye staining score >10 with TBUT ≤ 5 seconds *and* Schirmer I test score of ≤ 5mm/5 minutes).

We also recorded evidence of conjunctival inflammation, such as hyperemia, chemosis, conjunctival ulceration and/or sloughing, subconjunctival fibrosis, forniceal foreshortening, and symblepharon formation.[8] Co-existing lid diseases, such as blepharitis and obstructive meibomian gland dysfunction (**MGD**), and corneal pathology, such as superficial punctate keratopathy (**SPK**), filamentary keratitis, epithelial defect, microbial keratitis, corneal thinning and stromal opacification, were also documented. The results of additional tests, such as microbial culture and sensitivity testing, and conjunctival biopsy,[24] were recorded. We documented the local and systemic interventions for OSD, the durations of post allo-BMT follow-up and ocular follow-up, best-corrected visual acuity, and the status of the ocular surface and systemic indices of GVHD at the last follow-up examination.

B. Results

We identified 114 allo-BMT recipients who received full eye examinations by us during the period January 1995 to June 2002. All patients included in the study had allo-BMT performed through the Dana-Farber Cancer Institute–Partners Hematology-Oncology Program, Harvard Medical School, Boston MA. Two patients who had BMT elsewhere were excluded due to lack of data on their conditioning regimen and HLA matching. Because our focus was *chronic* OSD post-BMT, we excluded patients (N=23) whose follow-up post-BMT was less than 3 months, as the chronicity of their condition could not be assessed. We also excluded 27 patients who had no documented OSD in any of their eye evaluations, as our focus was exclusively on ophthalmic findings in these patients and the range and type of OSD post-BMT rather than the disease incidence. These latter patients had been referred for other ocular problems, and included 12 patients with posterior subcapsular cataracts, 7 patients who had ophthalmic complications restricted to the posterior segment, 4 patients with elevated intraocular pressure, and 4 patients with refractive problems.

Of the 62 patients who fit our criteria, 32 (52%) were women and 30 (48%) were men. The age at BMT ranged from 18 to 62 years (mean=40 years). The underlying diagnoses included chronic myeloid leukemia (N=29), acute myeloid leukemia (N=9), myelodysplastic syndrome (N=6), acute lymphocytic leukemia (N=5), aplastic anemia (N=4), non-Hodgkin's lymphoma (N=3), chronic lymphoid leukemia (N=2), multiple myeloma (N=2) and Hodgkin's lymphoma (N=2). Conditioning with total body irradiation (**TBI**) preceded BMT in 89% of the patients. The donor was a full HLA (6/6) match in all but 4 patients (94%) and was a blood relative in 31 patients (50%).

The onset of ocular symptoms occurred more than 3 months post-BMT in 84% of patients (N=52), whereas 16% (N=10) developed early symptoms that proceeded to chronicity. In all cases, the symptoms and signs persisted beyond the acute (0-3 months) post-BMT period. The majority of patients (94%, N=58) had their first post-BMT eye examination only after the onset of ophthalmic symptoms. The mean interval at which ocular symptoms developed post-BMT was 17 months (range = 0.25-101 months).

1. Initial Examination

The main presenting signs and symptoms are summarized in Tables 1-3. The visual acuity at presentation was