Graft-Versus-Host Disease

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17.1 Introduction

Allogeneic (genetically different, same species) hematopoietic stem cell transplantation (HSCT) is a curative therapy for a variety of hematological malignancies, autoimmune diseases, inherited disorders of metabolism, histiocytic disorders, and other malignant solid tumors [1–3]. The number and indications for HSCT continue to increase, with more than 30,000 procedures performed annually across the world [2]. The number of unrelated donor transplants, the most commonly performed transplant, is expected to double within the next 5 years due to improvements in techniques including donor leukocyte infusions and isolation of umbilical cord stem cells [2, 3].

The major histocompatibility complex contains the genes that encode tissue antigens, which is referred to as the human leukocyte antigen (HLA) region in humans [4]. Syngeneic

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transplantation, between identical twins, represents the optimal form of HSCT and, unlike other allogeneic donors, does not carry risk of GVHD [5]. Even with sibling donors, which are more likely than unrelated donors to be HLA-matched, 25–35 % of recipients develop GVHD [2, 5]. Despite HLA matching between a patient and donor (sibling or unrelated), substantial numbers of patients still develop GVHD because of differences in minor histocompatibility antigens that lie outside the matched HLA loci [2, 5].

GVHD remains the most frequent and serious complication limiting broader application of HSCT. Given the increasing number of transplant recipients, larger numbers of patients affected with GVHD are expected in the near future. As many recipients of HSCT become long-term survivors, their quality of life becomes increasingly important.

17.2 Etiology

Billingham formulated three requirements for the development of GVHD in 1966: the graft must contain immunologically competent cells, the recipient must express tissue antigens that are not present in the transplant donor, and the recipient must be incapable of mounting an effective response to eliminate the transplanted cells [6, 7].

GVHD develops when donor T cells respond to recipient tissue antigens secondary to mismatches between major or minor histocompatibility antigens between the donor and recipient [8]. Allogeneic HSCT is the most common setting for the development of GVHD.

17.3 Pathogenesis

Four important factors influence the pathogenesis of GVHD:

(A) *Source of hematopoietic stem cells*: Peripheral blood stem cells (PBSC) have largely replaced marrow for autologous and most allogeneic transplantations. Peripheral blood stem cells also contain T cells that increase the incidence of GVHD. A process called apheresis or leukapheresis is used to obtain PBSCs for transplantation [2, 3]. A more recent technique to obtain hematopoietic stem cells is the preparation of umbilical cord blood [2, 9]. In cases of urgent transplantation or if donors cannot be found, umbilical cord blood becomes an alternative. The establishment of a worldwide network for umbilical cord blood cell procurement, typing, and cryopreservation has resulted in a large collection and facilitated more than 7,000 unrelated transplants. Cord blood as a source of stem cells has several advantages: its transplantation requires less-stringent HLA matching than is required for that of peripheral blood or marrow, and mismatched cord blood cells are less likely to cause GVHD [10, 11].

(B) *Preparation of donor*: For 4 or 5 days before apheresis, the donor may be given granulocyte colony-stimulating factor (GCSF) to increase the number of stem cells in circulation. The stem cells are isolated from circulation based on the cell membrane expression of CD34+, a hematopoietic stem cell marker [12]. These peripheral blood CD34+ stem cells are capable of forming colonies of granulocytes/macrophages, erythrocytes, and other multipotential or immature progenitors. The CD34+ stem cells are frozen until they are infused to the recipient.

(C) *Preparation of recipient*: The recipient first receives a conditioning regimen consisting of chemotherapy, which is often combined with radiotherapy and T-cell-depleting antibody designed to immunosuppress the host in order to decrease the possibility of graft rejection and, when used to treat cancer, to reduce the number of malignant cells. This is followed by the infusion of donor cells [2].

(D) *Depletion of T cells*: Whereas bone marrow cells and GCSF-mobilized PBSCs are both enriched with hematopoietic progenitors, they also contain mature T cells that are responsible for graft rejection [2, 6, 7]. Three main strategies to deplete T cells and

decrease the incidence of GVHD have been proposed:

1. Selection of T cells ex vivo before transplantation
2. Positive selection of CD34+ stem cells ex vivo by immunomagnetic separation [12]
3. Antibodies against T cells in vivo [13]

These approaches showed substantial reduction of both acute and chronic GVHD. However, reduced frequency of severe GVHD is offset by high rates of graft failure, relapse of malignant disease, infections, and Epstein-Barr virus-associated lymphoproliferative disorders. Moreover, overall survival has not significantly improved when compared with use of non-T-cell-depleted bone marrow [12, 13].

17.4 Classification of GVHD

Graft-versus-host disease presents in an acute or chronic form. Historically, the acute and chronic forms were arbitrarily defined based on the time of onset since transplant (less than or more than 100 days, respectively) [2]. A clear distinction between acute and chronic forms of GVHD as originally described can no longer be delineated, given the alterations in the recipient's immunosuppression [2, 14]. In 2005, the National Institutes of Health working group sought to standardize the definitions of acute and chronic GVHD (Table 17.1). Currently, the diagnosis of chronic GVHD is based on specific signs, degree of organ involvement (mild, moderate, severe), laboratory data, or histopathological confirmation rather than time of onset since transplant (Table 17.2) [15].

17.4.1 Acute GVHD

Despite prophylactic measures, the incidence of aGVHD is estimated to be 40–60 % among patients receiving transplants from HLA-

Table 17.1 Categories of GVHD

Category	Time of symptoms after HSCT	Presence of acute GVHD features	Presence of chronic GVHD features
Acute GVHD			
Classic acute GVHD	≤100 days	Yes	No
Persistent, recurrent, or late onset acute GVHD	>100 days	Yes	No
Chronic GVHD			
Classic chronic GVHD	No time limit	No	Yes
Overlap syndrome	No time limit	Yes	Yes

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

Table 17.2 Signs of chronic GVHD

Skin	Poikiloderma, lichen planus-like features, sclerotic features, morphea-like features, lichen sclerosus-like features, often areas of depigmentation: hypopigmentation or hyperpigmentation
Nails	Nails dystrophy or loss
Hair	Alopecia, scaling
Mouth	Xerostomia, restriction of mouth opening from sclerosis, mucosal atrophy, pseudomembranes, and ulcers
Muscle, fascia, joints	Fasciitis, myositis, or joint contractures
Gastrointestinal/liver	Anorexia, weight loss, esophageal web or strictures, elevation of total bilirubin and liver enzymes
Lungs	Restrictive or obstructive defects on pulmonary function tests, bronchiolitis obliterans, pleural effusions
Kidneys	Nephrotic syndrome
Heart	Pericarditis
Bone marrow	Thrombocytopenia, anemia, neutropenia

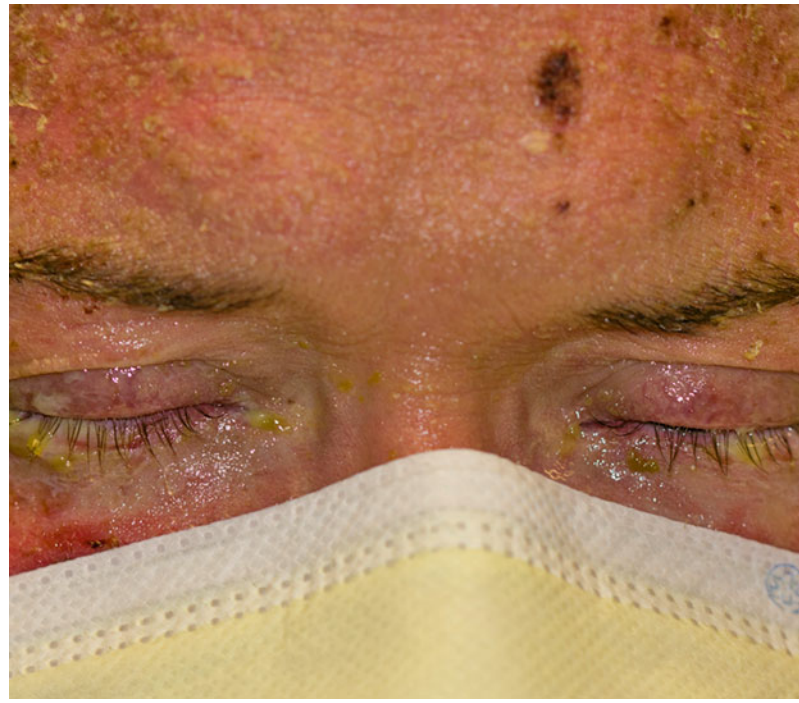

Fig. 17.1 Acute GVHD characteristically affects epithelial cells in the body. Periocular skin involvement is common as well as conjunctival chemosis and epithelial erosions in the lid margin epithelium

identical sibling donors and 75 % in patients receiving HLA-matched unrelated donors [16]. Acute GVHD is characterized by selective epithelial damage of target organs [17] such as skin, liver, and gastrointestinal tract within 14–42 days of infusion [14]. A "hyperacute" form of GVHD may occur within 14 days of infusion, in patients with severe HLA-mismatched donor or in those that have received inadequate GVHD prophylaxis [14]. Hyperacute GVHD is manifested by high fever and severe cutaneous component (generalized erythema with desquamation), in addition to hepatitis and intestinal symptoms; this form of GVHD may be rapidly fatal [15].

In ocular graft-versus-host disease, the histopathological changes are mainly seen in the conjunctiva and lacrimal gland tissue [18, 19]. As mentioned previously, aGVHD is primarily a T-cell-mediated process, and in the conjunctival tissue of patients with aGVHD-related pseudomembranous conjunctivitis, donor-derived mononuclear T lymphocytes have been detected [20] (Fig. 17.1).

17.4.2 Chronic GVHD

Patients who have received stem cells/bone marrow from an HLA-mismatched related donor or from an HLA-matched unrelated donor are at an increased risk of cGVHD [2]. Other factors that increase the risk of cGVHD include older recipients and those who have already experienced aGVHD [2]. The chronic form of graft-versus-host disease (cGVHD) has features resembling autoimmune disorders such as scleroderma, Sjögren syndrome, primary biliary cirrhosis, bronchiolitis obliterans, immune cytopenias, and chronic immunodeficiency. Symptoms usually present within 3 years after allogeneic HSCT and are often preceded by a history of acute GVHD [2, 5]. Manifestations of cGVHD may be restricted to a single organ or tissue or may be widespread (Table 17.3).

Dry eye is the most frequent ocular complication usually occurring approximately 6 months posttransplantation [21]. In chronic ocular GVHD, inflammatory destruction of the conjunctiva and lacrimal gland with fibrosis occurs

resulting in aqueous tear deficiency and damaged ocular surface [22] (Fig. 17.2). Extensive tissue destruction, tissue atrophy, and fibrosis of the tubuloalveolar glands and ducts in the lacrimal gland have been shown on histology [17].Chronic GVHD can lead to debilitating sequelae such as joint contractures, loss of sight, end-stage lung disease, or mortality from profound chronic immune suppression [2, 5].

17.5 Clinical Features: Ocular Surface Manifestations

17.5.1 Symptoms and Signs

Ocular cGVHD mimics other immunologically mediated inflammatory diseases of the ocular surface and there are no specific symptoms or clinical signs. Ocular manifestations, present in 60–90 % of patients with cGVHD, primarily affect structures of the anterior segment, mainly the lacrimal gland, meibomian glands, and conjunctiva [23]. Typical symptoms of cGVHD are dry eye, photophobia, foreign body sensation, irritation, burning, epiphora, redness, and blurriness [24].

Table 17.3 Diagnostic criteria for cGVHD

Distinction from acute GVHD
Presence of at least 1 diagnostic clinical sign of cGVHD
Presence of at least 1 distinctive manifestation confirmed by biopsy or other relevant tests
Exclusion of other possible diagnoses

17.5.2 Target Tissues

17.5.2.1 Lacrimal Gland

The lacrimal gland is an important ocular target for the pathogenesis of GVHD [21, 23, 25]. Fibrotic processes often affect the lacrimal gland reducing its secretory capacity or causing complete stasis with distended ductules and obliteration of ducts lumen, similar to bile duct damage seen in liver cGVHD [25]. Histological studies also showed extensive destruction, tissue atrophy, and fibrosis of the tubuloalveolar glands and ducts in the lacrimal gland with an increase in CD34+ stromal fibroblasts accompanied by mild lymphocytic infiltration [21].

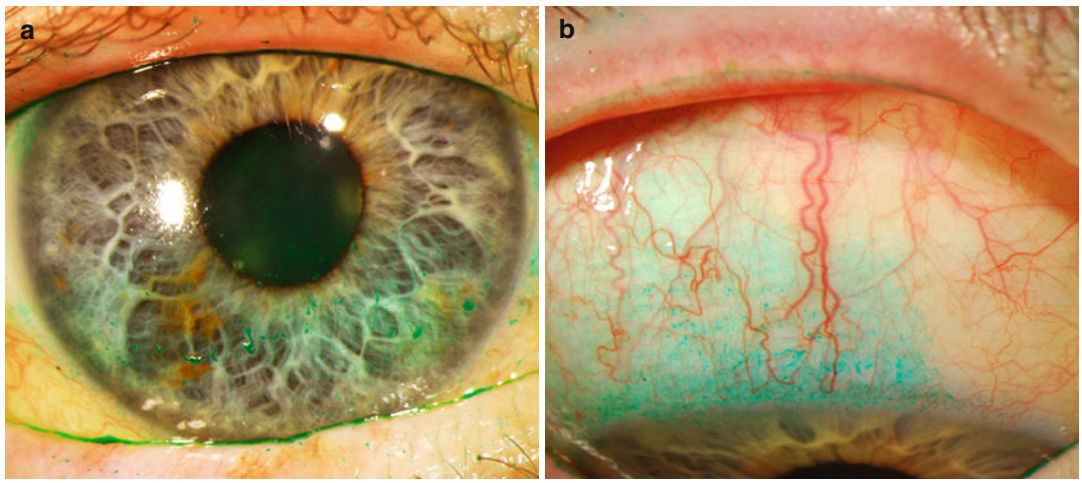

Fig. 17.2 Ocular GVHD manifests with different degrees of severity in the ocular surface. Lissamine green staining in the interpalpebral area of this patient affected with chronic ocular GVHD (**a**). The same patient with superior limbal keratitis shown by lissamine green staining in the superior limbal region (**b**)

17.5.3 Meibomian Glands

Besides aqueous tear deficiency, progressive decline of conjunctival goblet cells and the dysfunction of meibomian glands contribute to the overall breakdown of the ocular tear film causing severe keratoconjunctivitis sicca [23, 26]. In vivo confocal microscopy shows destruction of the ductal epithelia due to lymphocyte infiltration, sloughing of epithelial cells, pseudomembrane formation, and subsequent excessive fibrosis around the orifice, ducts, ductules, and acini of the meibomian gland; all these findings together may explain the development of meibomian gland disease [27].

17.5.4 Conjunctiva

Pseudomembranous conjunctivitis can rarely occur in cGVHD and is partly considered as an acute variant of GVHD [26]. Sterile inflammatory conjunctival involvement is a common finding, which can be accompanied by formation of pseudomembranes, loss of lashes, and stenosis or closure of the lacrimal punctum. Palpebral and subtarsal conjunctival scarring is seen in a number of patients, sometimes resulting in the formation of cicatricial lagophthalmos [26, 28].

17.5.5 Cornea

Corneal findings include punctate keratopathy, formation of mucus filaments, painful erosions, and eventually secondary corneal infections [26, 28]. Less frequently, sterile corneal stromal necrosis and perforations may occur [29]. Superior limbic keratoconjunctivitis in the setting of ocular chronic GVHD is believed to be more common in peripheral stem cell transplantation patients compared with bone marrow recipients [23].

17.6 Diagnostic Evaluation

Given the different target tissues and possible sequelae involved in ocular GVHD, the potential list of differential diagnoses is extensive. It is essential to evaluate the patient's medical history since the diagnosis of ocular GVHD is more likely in the setting of severe refractory dry eye disease, a decrease in Schirmer scores, and worsening ocular symptoms [23]. A full ophthalmological examination including best-corrected visual acuity and slit-lamp examination using vital dyes such as lissamine green, rose bengal stain, or fluorescein is needed to evaluate punctate keratopathy, corneal erosions, or ulcers. Additionally, a thorough subtarsal and meibomian gland inspection, evaluation of tear film breakup time, and a Schirmer test are essential in patients suspected of ocular GVHD [24]. According to Filipovich et al. [15], a diagnosis of chronic GVHD can be made by low Schirmer test values (without anesthesia) with a mean value of both eyes <5 mm at 5 min or a new onset of keratoconjunctivitis sicca by slit-lamp examination with mean values of 6–10 mm on the Schirmer test accompanied by distinctive manifestations in at least 1 other organ. Special diagnostics such as tear film osmolarity, corneal sensitivity testing, in vivo confocal microscopy for inflammatory cells, and photodocumentation can assist in therapeutic decisions and follow-up.

Slit-lamp examination of the lens should also be performed to assess for posterior subcapsular cataract, which commonly occurs secondary to steroid and/or radiation treatment. Systemic steroid therapy and topical steroid therapy also necessitate assessment for glaucoma including intraocular pressure measurements and visual field testing.

Posterior segment involvement such as CMV retinitis occurring in the setting of immunosuppression should be excluded [24]. Posterior scleritis, choroidal thickening, and serous detachments have rarely been observed in the acute or hyperacute GVHD [23].

It may also be beneficial to use quality of life questionnaires such as the Ocular Surface Disease Index to evaluate the extent of disease and the response to treatment [24].

17.7 Differential Diagnosis

The most common ocular manifestation of GVHD is keratoconjunctivitis sicca, which usually develops in conjunction with inflammatory

signs of the conjunctiva (conjunctival edema, chemosis, pseudomembrane formation) and chronic blepharitis [23, 26, 28]. Keratoconjunctivitis sicca primarily results from either aqueous tear deficiency or abnormal tear composition. The differential diagnosis of aqueous tear deficiency consists of autoimmune diseases such as Sjögrens, a multitude of medications such as diuretics and antihistamines, and any process that results in infiltration of the lacrimal gland including sarcoidosis, tumors, or postradiation fibrosis.

Cicatricial meibomian gland dysfunction along with the other changes described above can also occur in trachoma, ocular pemphigoid, and erythema multiforme. Other causes of meibomian gland dysfunction include seborrheic dermatitis, atopy, acne rosacea, and psoriasis.

17.8 Treatment of Systemic GVHD

17.8.1 Prevention of GVHD

Prevention of acute GVHD by the use of pharmacologic prophylaxis is an integral component to the management of patients undergoing allogeneic HSCT [5, 14, 26]. A regimen based on methotrexate with a calcineurin inhibitor, a cytoplasmic enzyme important for activation of T cells, is standard practice and is recommended in different studies [14, 16, 26]. The most widely used regimen includes a combination of either cyclosporine or tacrolimus with a brief course of methotrexate [14, 26]. For higher-risk groups (such as mismatched donors, older patients), more intensive immunosuppression is often required [2, 5, 26].

17.8.2 Treatment of Established GVHD

Although many therapeutic options have been used in the management of ocular GVHD, adequate treatment remains a challenge. The management is guided by a multidisciplinary approach, including adjustment of immunosuppression and aggressive supportive care. The treatment approach should include multiple strategies (topical and oral medications, surgery, environmental control, and systemic immunosuppression). Communication with the transplantation team is crucial in the optimal management of GVHD patients. Symptomatic mild cGVHD may often be treated with local therapies alone (e.g., artificial tears, topical steroid, serum drops). However, in patients with cGVHD that involves three or more organs or severe damage in any single organ, systemic immunosuppressive therapy may be considered.

17.8.3 Treatment of Ocular GVHD

Patients with ocular symptoms need close ocular supportive care focused on improving ocular surface moisture and decreasing ocular surface inflammation by using multiple available treatments. However, treatment of severe ocular cGVHD is challenging.

17.8.3.1 Topical Lubricants

The traditional treatment for dry eye symptoms consists of topical lubricants [30]. Data is not available on the efficacy of specific artificial tear medications in ocular GVHD. Although artificial tears and lubricants are needed to lubricate the ocular surface, ocular cGVHD is a complex problem of the ocular surface with multiple dysfunctional tear components. Punctal plugs can also be considered to improve the benefit of topical lubricants.

17.8.3.2 Topical Corticosteroids

Corticosteroids remain essential for controlling active chronic graft-versus-host disease. Systemic steroids represent the mainstay in the treatment of acute (exacerbations of) cGVHD but not enough data are available on the efficacy of topical steroids in ocular GVHD. In a small study of seven patients with conjunctival GVHD, resolution or improvement of the conjunctival signs was achieved using topical corticosteroids but the signs of KCS remained unchanged [31]. Patients receiving topical corticosteroids should be monitored for adverse effects. In presence of corneal epithelial defects, stromal thinning, or infiltrates, topical corticosteroids are contraindicated.

17.8.3.3 Topical Cyclosporine A

Cyclosporine A is a cyclic polypeptide produced by the fungus Tolypocladium inflatum Gams. Cyclosporine 0.05 % ophthalmic emulsion (Restasis, Allergan, Inc., Irvine, CA) has been FDA-approved for treatment of dry eye disease since 2003. Cyclosporine A emulsion has shown to decrease the number of activated T cells in the ocular surface, increase the goblet cell density of the conjunctiva, decrease epithelial cell apoptosis, and reduce proinflammatory cytokines [32]. In a small study of eight cGVHD patients treated with cyclosporine 0.05 % ophthalmic suspension twice a day for at least 3 months, researchers noted mean Schirmer score increases, tear breakup time improvement, and subjective symptoms improvement [33]. In another study of only 16 patients (32 eyes) with GVHD, dry eye symptoms improved in 62.5 % of patients and corneal fluorescein staining improved in all eyes after a mean follow-up of 90 days [34]. Baptista Malta reported a retrospective study with 105 patients of whom 43 patients developed cGVHD. All patients were initially started on topical cyclosporine before the HSCT. They conclude that cyclosporine is helpful in decreasing the incidence and severity of dry eyes in patients who are under topical cyclosporine before the HSCT [35].

Although beneficial effect of topical cyclosporine on ocular GVHD has been documented in several studies comprised of small number of cases, there is, at present, no large randomized study that clearly suggests its usefulness.

17.8.3.4 Tacrolimus

FK506 (tacrolimus) is a macrolide antibiotic extracted from the soil fungus Streptomyces tsukubaensis and its mechanisms of action and pharmacokinetics are similar to cyclosporine, although the immunosuppressive potency of tacrolimus in vitro is 50–200 times greater. Although the beneficial effect of systemic tacrolimus on ocular GVHD has been observed [16, 36], topical administration might be a better treatment option because of the adverse effects associated with its long-term systemic administration. Except for two case reports in which ocular GVHD was successfully treated, not enough data are available on the use of topical tacrolimus [37, 38].

17.8.3.5 Autologous Serum Eyedrops

Fox et al. described serum drops as a tear substitute free of preservatives in 1984 [39]. Autologous serum contains vitamin A, epidermal growth factor, fibronectin, and transforming growth factor beta, which all are needed for a healthy ocular surface epithelium [40, 41]. The efficacy and safety of autologous serum drops were investigated in a small study of 14 patients with ocular GVHD and severe cGVHD not responsive to conventional artificial tears therapy. After 4 weeks of treatment, significant improvement was observed in dryness symptoms and fluorescein scores and also in rose bengal staining and tear breakup time [41]. The improvement was noted in all patients at the 4-week follow-up [41]. The risk of contamination and subsequent infection forms a possible complication of autologous serum drops.

17.8.3.6 Contact Scleral Lenses

In patients with cGVHD affecting the ocular surface, two different types of lenses can be used, the bandage soft lens and the scleral rigid lens. The fluid-ventilated, gas-permeable scleral lens has been effective in mitigating symptoms and resurfacing corneal erosions in the treatment of moderate and severe ocular surface disorders of multiple etiologies. The fluid-filled reservoir shields the cornea from blink trauma, noxious environmental stimuli, and inflammatory mediators in the tears. The body-temperature saline reservoir also prevents corneal cooling and nerve firing that occurs during the inter-blink intervals [42].

One of the scleral lenses used (Boston Scleral Lens Prosthetic Device) was approved for the management of corneal disorders by the Food and Drug Administration in 1994. Takahide published a retrospective review on 9 patients fitted for refractory ocular surface disease secondary to cGVHD [43]. Contact lens fitting was prompted by debilitating ocular discomfort, visual impairment, or keratopathy. Some of the

patients evaluated were using artificial tears, cyclosporine eyedrops, punctal plugs, autologous serum tears, and moisture chamber eyewear. All patients reported improvement of ocular symptoms, reduced use of topical lubricants after fitting, and improvement in the ocular surface disease index [43].

The same group published results of 33 consecutive patients with severe dry eye from cGVHD, unresponsive to conventional therapy. Ninety-four percent of patients reported improvement in photophobia in the worse eye. Ninety-seven percent of patients reported improvement in life quality with no complications noted during the follow-up period [44]. Schornack reported the successful use of the Jupiter scleral contact lens (Medlens Innovations, Front Royal, VA or Essilor Contact Lens, Inc., Dallas, TX) in the management of 10 eyes of 5 patients with cGVHD. All patients had improvement in symptoms and some improved visual acuity. Jupiter lenses are commercially available in the US and may therefore be more accessible and affordable to patients who could potentially benefit from this treatment [45].

Although scleral lenses are maybe the most important tool in the armamentarium, their use is not widespread. Published data suggest that scleral rigid gas-permeable lenses are an important therapeutic option for patients with recalcitrant ocular surface compromise and debilitating symptoms. High cost, inadequate fitting, poor tolerance by some patients, and discomfort with blinking in the presence of severe meibomian gland disease and keratinization are some of the drawbacks. To our knowledge, no comparative prospective study has evaluated the different types of scleral lenses available.

17.9 Follow-Up

According to the participants in the German/Austrian/Swiss Consensus Conference on clinical practice in chronic GVHD, recommendations for monitoring patients are as follows: (1) a baseline ophthalmological workup including the Schirmer test before HSCT, (2) a screening examination at day 100–200 after HSCT, and (3) an ophthalmological assessment in case of ocular symptoms or any other manifestation of GVHD. An ophthalmologist should complete these examinations. This protocol allows for (1) a baseline examination to detect progressive KCS earlier, (2) diagnosis of ocular cGVHD earlier, and (3) an early start with treatment to prevent excessive scarring and inflammation processes that may lead to serious complications ultimately improving symptoms and quality of life.

17.10 Prognosis of Ocular GVHD

A few reports have studied the long-term prognosis in patients affected with ocular cGVHD. Sales et al. in a case series of 49 patients reports that in the long term, many patients with cGVHD may experience improved dry eye symptoms as a result of effective treatment. Although only nine patients completed this 3-year prospective case series, stable visual acuity, tear production, and lissamine green staining and a statistically insignificant improvement in dry eye symptoms were reported [46]. A recent study has reported that the incidence of dry eye was significantly higher in the recipients of peripheral blood stem cells than those receiving bone marrow or cord blood.

Another retrospective cohort study reported that of 56 patients with cGVHD, 39 % developed symptoms of photophobia, irritation, and foreign body sensation [47]. Over time, patients required fewer topical medications to control their symptoms; only 5 % of patients required more than two medications for dry eye disease management at the end of follow-up [47].

In contrast, Ogawa et al. series of 53 patients suggested that the symptoms of dry eye, including ocular fatigue, foreign body sensation, pain, blurring, photophobia, and epiphora, were almost universally worse among 22 participants at 30 months after HSCT in comparison to before HSCT [48].

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