OCULAR MORBIDITY IN BONE MARROW
AND PERIPHERAL BLOOD STEM CELL
TRANSPLANT RECIPIENTS
OCULAR MORBIDITY IN BONE MARROW AND PERIPHERAL BLOOD STEM CELL TRANSPLANT RECIPIENTS

A dissertation submitted in partial fulfillment of the MS Branch III (Ophthalmology) examination of the Tamil Nadu Dr MGR Medical University to be held in March 2007
DECLARATION

I hereby declare that the investigations that form the subject matter of this thesis was carried out by me under the guidance of Dr. Pushpa Jacob, Professor of Ophthalmology, Christian Medical College, Vellore. This has not been submitted in any other university in part or in full.

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CERTIFICATE

This is to certify that this dissertation entitled “Ocular morbidity in post bone marrow and peripheral blood stem cell transplant recipients” is bonafide work done by Dr Anupriya Arthur in partial fulfillment of the rules and regulations for M.S.Branch III (Ophthalmology) examination of the Tamilnadu Dr MGR Medical University, Chennai, to be held in March 2007.

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INTRODUCTION

The first successful transplantation of allogenic haematopoietic cells was performed in 1968 in three children with congenital immune deficiency. Since then thousands of patients have received haematopoietic stem cell transplantation. Bone marrow transplantation has now become the treatment of choice for a wide variety of hematological and non hematological disorders such as aplastic anemia, hematological malignancies, transfusion dependent congenital anemias and some metabolic diseases.

The source of stem cells can be from bone marrow, peripheral blood or cord blood.

BMT uses ablation of the patient’s own bone marrow with cytoreductive chemotherapeutic agents and with total body irradiation followed by transplantation of the donor marrow to reconstitute the patient’s hematologic function. The eyes are generally not shielded during total body irradiation because they are a potential site of leukaemia relapse. Subsequently the patient has to be maintained on a prolonged immunosuppressive regimen to prevent rejection of the transplanted bone marrow.

In general haematopoietic stem cell transplant can be classified into 3 different types

1. Allogenic transplant – donor marrow is harvested from HLA compatible donor
2. Syngenic transplant – donor marrow is harvested from HLA compatible monozygotic twin
3. Autologous transplant - patients own bone marrow is harvested prior to induction therapy and later restored after chemotherapy and total body irradiation has been completed.

Complications following BMT are not uncommon and involve various organs like lungs, GIT and the eye. The underlying causes are multifactorial. These includes side effects of the preparative regimens such as high dose chemotherapy, steroid treatment and irradiation as well as graft versus host reaction. The major systemic complications post transplantation are infections and graft versus host disease (GVHD) which can be acute or chronic. In GVHD the lymphocytes of the immunocompetent donor mount an immunological attack on the immunoincompetent host. Two distinct clinical syndromes of GVHD have been described, acute and chronic. Acute GVHD clinically presents within the first 100 days of transplantation as an acute exanthematous dermatitis, enteritis and hepatitis. In contrast chronic GVHD occurs later than 100 days. It resembles an autoimmune illness with scleroderma like involvement of the skin, dacyrooadenitis, chronic liver dysfunction and profound immunodeficiency.

Ocular complications following BMT are common. The most common anterior segment complications are keratoconjunctivitis sicca, cataract and corneal ulcers. Posterior segment complications include vitreous hemorrhage, microvascular retinopathy, optic disc edema and fungal and viral retinitis. Infectious and hemorrhagic lesions can occur as a consequence of transient pancytopenia immediately following the transplant. The infectious complications include fungal endophthalmitis, infectious keratitis and...
herpes zoster ophthalmicus. Hemorrhagic complications include subconjunctival hemorrhage and intraretinal and vitreous hemorrhage.\textsuperscript{5}

Ocular complications are common, but they are often underreported and under diagnosed due to lack of awareness and because of other life threatening systemic complications that overshadow them. Even though most of these complications do not lead to blindness, they can lead to significant ocular morbidity if appropriate treatment is not promptly initiated.

There is no data in this field from the Indian subcontinent. This study aims to evaluate the presence of ocular morbidity in patients undergoing bone marrow transplantation and peripheral blood stem cell transplantation.
AIMS

To document the presence of ocular morbidity in patients on follow up after bone marrow or peripheral blood stem cell transplantation.


**LITERATURE REVIEW**

Allogenic bone marrow transplant is an important treatment option for both malignant and non malignant neoplasms of the bone marrow including leukaemias, lymphomas and severe aplastic anemia.\(^5\)

Allogenic bone marrow transplantation (BMT) from an HLA-identical sibling is effective therapy for patients with bone marrow failure states and those with hematologic malignancies. However, only a minority of them will have an HLA-identical sibling donor. Unrelated matched or partially mismatched donors have been used successfully for patients lacking a related donor. Even though results with allogenic transplants using unrelated donors are encouraging, the incidence of complications including graft-versus-host disease (GVHD) and graft rejection or late graft failure is increased compared to HLA identical sibling transplants. The combination of cyclophosphamide and total body irradiation (TBI) has been used as an effective preparative regimen for allogenic transplants.\(^6\) By this *conditioning regimen* the patients own bone marrow is destroyed. The purpose of the regimen is to eradicate all malignant cells and to suppress the host immune response. The donor marrow is then transplanted to repopulate the host bone marrow thereby re-establishing the haematologic function.
Depending on the source of the stem cells, transplantation include peripheral blood stem cell transplant, bone marrow transplantation and cord blood transplantation. The technique of BMT consists of sterile removal of bone marrow from the iliac crest. The marrow is intravenously infused into the recipient. Subsequently the patients are maintained on a prolonged immunosuppression to prevent rejection of the transplanted bone marrow cells.

In Peripheral blood stem cell transplantation a variety of mobilization techniques are used to increase the number of stem and progenitor cells circulating in the peripheral blood. After mobilization, an apheresis machine collects the cells. After venous blood is collected and processed through the apheresis machine, the nontargeted components are returned to the patient.

In general bone marrow transplant can be classified into 3 different types

4. **Allogenic transplant** - using an HLA compatible donor

5. **Syngenic transplant** - HLA compatible monozygotic twin is the donor

6. **Autologous transplant** - Patients own bone marrow is used. Prior to induction therapy patients marrow is harvested and later restored after chemotherapy and TBI has been completed.

Subsequently following allogenic transplantation the patient has to be maintained on a prolonged immunosuppressive regimen to prevent rejection of the transplanted bone marrow.
The major systemic complications post transplantation are infections and graft versus host disease.9

**Graft versus host disease:**

In graft versus host disease lymphocytes of the immunocompetent donor mount an immunologic attack on the now immunoincompetent host.9 GVHD can be of two types acute and chronic.

**Acute GVHD** occurs within hundred days of transplantation in 30 to 60% of histocompatible sibling matched allografts. Mortality directly or indirectly due to acute GVHD may reach 50%. It classically presents as an acute exanthematous dermatitis, enteritis or hepatitis.11

**Chronic GVHD** develops in 30 to 50% of patients approximately 3 to 6 months after transplantation. It resembles an autoimmune illness with scleroderma like involvement of the skin, dacryoadenitis, chronic liver dysfunction and profound immunodeficiency with recurrent bacterial infections.12 Those at risk for chronic GVHD include older patients and those with previous acute GVHD.

Peripheral blood haematopoietic stem cell transplants have been shown to result in more rapid engraftment than standard bone marrow transplants and have better 2 year survival rates.10 But the rapid engraftment by itself in these transplant recipients
could lead to chronic GVHD and late systemic fungal and cytomegalovirus (CMV)
infection.\textsuperscript{10}

**Pathogenesis:**

Recognition of allogeneic difference by competent immunogenic cells is the
central event of GVHD.\textsuperscript{9} GVHD occurs when immunocompetent transplanted marrow
cells target antigens on the surface of recipient cells.

The first step in the development of GVHD is the **recognition** of host peptides by
allotransplanted immune cells. A co stimulatory signal determines whether peptide
recognition will lead to full or partial **activation** of an immunologic response.\textsuperscript{13}
**Secretion** of interleukin 2 (IL 2) leads to clonal expansion and proliferation of T cells. T
cells and monocytes in turn release cytokines, TNF alpha and interferon gamma which
recruit other T cells and natural killer cells.\textsuperscript{14} In support of this both CD4 and CD8
lymphocytes can be found in GVHD lesions.

**Dysregulation of the intrinsic cytokine network is a primary cause for the
induction and maintenance of GVHD.**\textsuperscript{15}

Antin and Ferrara proposed that GVHD after allogenic BMT may be
pathophysiologically characterized as a cytokine storm comprising three steps.\textsuperscript{16} The
initial step involves damage to the host tissue – skin, intestinal mucosa and liver caused
by radiation and / or chemotherapy during the conditioning regimen leading to the
production of proinflammatory cytokines such as IL-1 and tumor necrosis factor alpha (TNF \( \alpha \)). These in turn cause increased expression of HLA alloantigens and adhesion molecules on the surface of the host cells leading to activation and proliferation of mature donor T cells.

In the acute or suppurative form of GVHD the principal T cell response is a helper T cell type 1 or an inflammatory response with production of IL2 and interferon alpha. These cytokines activate additional donor and residual host mononuclear cells and macrophages resulting in the secretion of IL1, TNF alpha and other cytokines and consequent amplification of the pathogenic cycle.

The chronic or stimulatory form of GVHD is characterized by increased immunoglobulins E synthesis and exaggerated lymphoproliferative production of IL4 and IL10 by helper T cells.

One approach taken to prevent the cytokine storm after allogenic BMT has been to deplete donor T cells from the graft before infusion into the host. Although this maneuver reduces the risk of subsequent development of GVHD it concomitantly impairs the engraftment of donor cells and increases the risk of relapse of malignancy. The latter phenomenon has been attributed to the depletion of the cell mediating the so called graft vs host reaction. The exact identity of these cells and their relationship to those mediating GVHD remains unclear.

**Systemic manifestations:**

GVHD is manifested primarily by symptoms and signs associated with skin, GIT and liver.\(^{17}\) Cells reacting in an autoimmune fashion produce abnormal pattern of
cytokines which stimulate collagen production by fibroblasts. Both the B and T subsets of lymphocytes are altered qualitatively and quantitatively. However in severe GVHD bone marrow suppression may also occur. 60 to 80% of patients with acute GVHD will go on to develop chronic GVHD.24 25% of those who do not have acute GVHD go on to develop chronic GVHD. Acute and chronic GVHD differs in its distribution of target organs and its clinical presentation.18 Acute GVHD primarily affects the skin, liver and GIT.19

**Skin**

Mild acute GVHD of the skin presents as erythema and the severity increases as the percentage of body surface area involved increases. In severe cutaneous acute GVHD there is bulla formation and desquamation. The pathogenesis is immune mediated attack on the skin epithelium by the donor lymphocytes.

Staging of skin involvement in acute GVHD

Stage 1 - less than 25% of total body surface area

Stage 2 - 25-50% of total body surface area

Stage 3 - greater than 50% of total body surface area

Stage 4 - bulla formation
More than 90% of patients with chronic GVHD have cutaneous abnormality. Two predominant forms have been noted. One type is similar to lichen planus and the other resembles morphea.

Liver

The organ next commonly affected by acute GVHD is the liver. The earliest abnormality is a rise in conjugated bilirubin and the alkaline phosphatase level reflecting underlying damage to the bile canaliculi. In chronic GVHD cholestasis is common.

GIT

Gastrointestinal tract is the third most commonly affected organ. It can be the most severe and is refractory to treatment. Symptoms include abdominal cramps and diarrhea, which may exceed ten liters per day and may result in severe dehydration. The diarrhea is seedy representing epithelial desquamation. Severe cases can have haematochezia. In chronic GVHD enteritis is uncommon. Secretory diarrhea and fat malabsorption can occur.

Clinical staging of liver involvement is based on elevation of liver enzymes and bilirubin levels, while staging of GIT involvement is based on volume of diarrhea.

Treatment for systemic GVHD

Corticosteroids are the mainstay of therapy. Dosing is titrated according to the grade and severity of GVHD. It can range from one milligramme per kilogramme to
three milligramme per kilogramme per day. Cyclosporine can also be used as primary therapy. Thalidomide has also been described. Chronic GVHD if left untreated has an overall survival rate of 18%. 

**Prevention of GVHD**

One approach to prevent GVHD is to use antibodies that recognize antigens expressed on T cells. With this acute GVHD develops in less than 10% of patients but engraftment fails to achieve in 20%. Another approach is induction of post transplant immunosuppression with a combination of Methorexate and Cyclosporine. With this incidence of GVHD has decreased from 50% to 20%.

**Ocular Morbidity in Bone Marrow Transplantation**

Ocular morbidity is divided into two groups, depending on whether they occur in the acute phase or in the chronic phase.

**Acute phase complications:**

1. Pseudomembranous conjunctivitis
2. Corneal ulcer
3. Episcleritis
4. Secondary choroidal detachment
5. Secondary glaucoma
6. Cytarabine induced keratitis
7. Herpes simplex virus infections
Chronic phase complications:

1. Dry eye
2. Meibomian gland dysfunction
3. Retinal hemorrhages
4. Aseptic conjunctivitis
5. Lagophthalmos
6. Corneal thinning
7. Corneal melting
8. Nasolacrimal duct obstruction
9. Prolonged corneal ulcer
10. Calcareous corneal degeneration
11. Optic disc edema
12. Cotton wool spots
13. Cataract

Acute Phase complications

Pseudomembranous conjunctivitis can occur secondary to acute GVHD. Conjunctival involvement is a marker for severe systemic involvement in GVHD. Conjunctival GVHD presenting with pseudomembrane formation results from loss of the conjunctival epithelium.26

Herpes Simplex keratitis although rare can occur as an infectious complication. Approximately 80% of herpes infection involve the oral cavity. In the eye it tends to
occur early, usually during the first month after SCT and is due to the result of the virus reactivation.

**Cytarabine induced keratitis** is due to high concentration of the drug in the tears. It is usually noted four to seven days after commencement of therapy with Cytosine arabinoside.\(^{27}\) It presents with symptoms of foreign body sensation, photophobia and blurred vision. The conjunctiva shows hyperaemia and chemosis. Corneal changes varies from refractile epithelial microcysts, central punctate erosions, sub epithelial opacities and mild stromal oedema. Topical steroids are the treatment of choice. Steroids are given till all the symptoms and signs disappear.

**Chronic phase complications:**

**Meibomian gland dysfunction** is frequently associated with severe dry eye and is related to chronic GVHD. The evaluation of meibomian gland dysfunction is helpful for the diagnosis of dry eye.\(^{28}\)

**Recurrent corneal perforation** and acute calcareous degeneration that can be recalcitrant to medical and surgical treatment can occur in chronic GVHD as a complication of keratoconjunctivitis sicca.\(^{29}\)

**Cataract** after SCT usually develops within 3 to 5 years. Cataract genesis is caused by a combination of pretreatment with antimitotic agents, exposure to radiation
during the conditioning process and prolonged use of systemic steroids. Cataract is usually posterior subcapsular.

Lagophthalmos, corneal thinning, corneal melting, nasolacrimal duct block and chronic dacrocystitis can be seen as late complications. Acute anterior uveitis can develop for up to 20 months after transplantation.

**Retinal hemorrhages** is related to GVHD, vasculopathy, CMV retinitis or recurrence of leukemic disease.

**Anterior segment complications**

The most common anterior segment complications are keratoconjunctivitis sicca, cataract. These are more common in patients in patients with GVHD\textsuperscript{26} and is described in detail later.

**Posterior segment complications**

The common posterior segment complications are vitreous hemorrhage, microvascular retinopathy, optic disc edema and fungal and viral retinitis.

**Retinal complications of bone marrow transplantation**

Posterior segment complications are less frequently encountered, but they can have significant visual consequences and implications. About 12% of patients can develop posterior segment complications.\textsuperscript{30}
They are of 3 types\textsuperscript{31}

1. Micro vascular retinopathy
2. Infection
3. Hematological complications

**Bone Marrow Transplant retinopathy** was first reported in 1983. It usually occurs within 6 months of BMT. It can occur as early as 3 months or as late as 62 months after BMT. Diabetes can facilitate the development of BMT retinopathy by contributing to the ischemic microvasculopathy. There are no known predictors like age, gender and race for this complication.

**Clinical features of BMT Retinopathy**

Patients present with decreased visual acuity, field deficit or both. Retinal findings are typically bilateral and symmetrical. Clinical findings include multiple cotton wool spots, telangiectasias, microaneurysms, macular edema, hard exudates and retinal hemorrhages.

Occlusive microvascular retinopathy has been described after BMT with retinal oedema, hemorrhage, soft exudates and neovascularisation in the posterior pole and peripheral fundus. It regresses and cicatrices with oral steroids. The visual prognosis depends on the foveal involvement of the retinopathy.\textsuperscript{32} **Fluorescein angiogram** often reveals capillary non perfusion and dropouts. Intraretinal microvascular abnormality,
microaneurysm and fluorescein leakage around the fovea consistent with macular edema can be seen.

Bilateral optic disc oedema may also be present. This can be due to microvascular retinopathy or to cyclosporine induced neurotoxicity.

**Pathogenesis:** The exact cause for BMT retinopathy is yet to be ascertained. Cyclosporine toxicity, total body irradiation and conditioning chemotherapy have been implicated.

*Cyclosporine* is a potent immunosuppressive agent. It can cause endothelial cell injury. Other side effects are nephrotoxicity, hypertension, seizures, encephalopathy, cortical blindness, cerebellar and spinal syndromes and raised intracranial tension. But it has not been demonstrated to cause BMT retinopathy in autologous or syngenic bone marrow recipients or in renal transplant patients. Drugs such as Cisplatin, Carmustin and Cyclophosphamide can cause ocular side effects including papillodema, optic neuritis, visual field defects and cortical blindness. Cyclosporine induced retinal toxic blindness can occur.

*TBI* damages the retinal microvasculature and may lead to ischemic vasculopathy. Modifying factors such as total dose of irradiation and the time interval between radiation and bone marrow ablation are important. The incidence and severity of BMT retinopathy correlate with high total body irradiation and a short time interval between
radiation and BMT. Therefore irradiation is not the sole factor but it appears to be another contributory factor in the development of BMT retinopathy.

BMT retinopathy and radiation retinopathy have similar clinical features including multiple cotton wool spots, telangiectasia, microaneurysms, macular edema, hard exudates and retinal hemorrhages.

But there are definite differences between the two:

1) BMT retinopathy is generally reversible where as radiation retinopathy is progressive. In fact BMT retinopathy does not progress beyond the ischemic microvascular stage.

2) Radiation retinopathy is often refractory to treatment.

3) BMT retinopathy is usually observed within 6 months of BMT but radiation retinopathy manifest approximately 18 months after the treatment.

Patients with BMT retinopathy usually have a good prognosis – the retinopathy typically resolves within 2 to 4 months after cessation or lowering of the dosage of cyclosporine with or without the use of systemic prednisolone. In one report 69% of patients had complete resolution of the retinal findings and 46% of patients fully recovered their baseline visual acuity. Because of the relatively favorable prognosis and non progressive nature of BMT retinopathy aggressive treatment is not necessary.

Infection
Infections in the post bone marrow transplant period is a major cause for mortality in recipient patients. However ocular infections are relatively uncommon after haematopoietic stem cell transplantation. Ocular infections usually affects the posterior segment and the incidence is around 2%.

Viral infections:

*CMV retinitis* is seen in about 1% of patients after BMT. In solid organ transplantation the incidence is 2 to 15%. Repeated treatment with antithymocyte globulin may lead to immune dysfunction that could increase the likelihood of CMV retinitis. Certain immunosuppressive agents such as mycophenolate mofetil has been associated with increased risk of systemic CMV infections in BMT. Visual outcome from CMV retinitis can be devastating. In most cases total blindness occurs, and is seen in three out of five patients treated adequately with antiviral regimen. CMV retinitis is more in HLA matched unrelated donor transplants than in HLA matched related sibling transplants. It responds well to antiviral agents. The prophylactic use of Valacyclovir for CMV infection in BMT has been proposed. Treatment is with Foscarnet and intraocular injection of Gancyclovir.

Another cause of viral retinitis is *Herpes zoster*. Clinical features of herpes zoster retinitis are similar to those for acute retinal necrosis. The infection typically responds well to intravenous Acyclovir therapy.

Fungal infections:
Fungal infection is not an uncommon posterior segment complication. In one study fungal retinitis and endophthalmitis were the most common intraocular infections after bone marrow transplantation. Among them Candida and Aspergillosis are common.30

Fungal infections occur early after bone marrow transplantation with a median time of fifty seven days. In solid organ transplants Aspergillus retinitis is more common.47,48 The primary focus of Aspergillus is subretinal or subretinal pigment epithelium. Vitreous biopsy may not yield positive results in Aspergillosis. Disseminated Fusarium infection with secondary fungal endophthalmitis can occur.49

Toxoplasmic retinochoroiditis 50

This is a reactivation of the existing ocular toxoplasmosis. Infection may also represent primary ocular disease. Toxoplasmic retinochoroiditis typically occur within three to six months and can be either unilateral or bilateral. With appropriate antibiotic therapy it can usually be controlled.

Hematological complications

In the early post transplant period hematological abnormalities including anemia, hyperviscosity syndromes and thrombocytopenia are common due to the bone marrow aplasia and chemotherapy 51,52. These changes predispose to vitreous hemorrhage, intraretinal hemorrhages and other hemorrhagic complications.53,54 Thrombocytopenia is
the most important factor in the development of hemorrhage. The incidence is about 3.5%. The majority of hemorrhagic complications are observed six months after BMT with the median time of 51 days.38

Other complications:

Central serous choreoretinopathy (CSCR) is more common after solid organ transplantation.31 Pathogenesis of CSR is believed to be associated with combined effects of high dose corticosteroids, emotional stress, systemic hypertension and cyclosporine. There may be also retinal pigment epithelial changes caused by choriocapillaries ischemia leading to serous retinal detachment. Visual prognosis is generally good and the treatment of photocoagulation may be needed only in refractory cases.

Bilateral optic disc edema may occur in 2.8%.30 Optic disc oedema is due to cyclosporine related toxic effects or increased pressure or both. Cyclosporine induced retinal toxic blindness after BMT can occur.55

Ocular manifestations of graft versus host disease

Because of other life threatening systemic complications in patients with GVHD, ocular manifestations may often be overlooked. This at least partially explains the sparse documentation in literature of ocular complications in this disease. Ocular features occur in approximately 60 to 80% of patients with GVHD.56 Ocular problems are
uncommon in acute GVHD, however ocular manifestations like keratoconjunctivitis sicca, sterile conjunctivitis, cicatricial lagophthalmos, cataracts and retinal micro vascular occlusive disease can occur due to chronic GVHD.

Dry eye associated with chronic GVHD is the most frequent ocular complication after SCT (40 - 60%) followed by meibomian gland dysfunction (48%) and retinal hemorrhage (35 to 40%).\textsuperscript{23} GVHD can involve any part of the eye

\textbf{Lids}\textsuperscript{57}

1. Dermatitis, acute and chronic
2. Lagophthalamos and ectropion from chronic lid inflammation
3. Loss of cilia

\textbf{Lacrimal apparatus:} Decreased aqueous secretions

\textbf{Conjunctiva}

1. Conjunctivitis
2. Xerosis secondary to decreased tears

\textbf{Cornea}

1. Superficial punctate keratitis
2. Persistent epithelial defect
3. Ulceration – infectious / sterile

\textbf{Uvea}

1. Iritis
2. Iridocyclitis
3. Choroiditis
**Posterior Segment Complications**

1. Microvascular retinopathy,
2. Intraretinal hemorrhage
3. Vitreous hemorrhage

**Lids**

Lids may be involved as part of the acute or chronic systemic skin changes associated with GVHD. Chronic lid inflammation may lead to lagophthalmos and ectropion. Loss of cilia is common with generalized skin involvement.

**Keratoconjunctivitis sicca**

Dry eye as a result of lacrimal gland dysfunction is one of the commonest manifestation of chronic GVHD. Even in patients with acute GVHD without ocular complications there is an increased risk for developing dry eye in the later stages.\textsuperscript{58} In most cases, the severity of the systemic chronic GVHD correlates with the severity of the dry eye.

**Incidence**

Dry eye after SCT has an incidence of 40 - 60\%.\textsuperscript{23} In a multicentric retrospective cohort study dry eye syndrome developed in 19\% of patients between 3 and 127 months after BMT. In this study 69\% with dry eye syndrome had systemic GVHD, compared with 30\% without dry eye.\textsuperscript{59}
Approximately half the patients who undergo SCT develop dry eye 6 months later. Severe dry eye resembling Sjogren’s syndrome progress rapidly after the onset of symptoms in the majority of these patients. The median time from transplantation to diagnosis of dry eye was 171 ± 5.9 days.

Pathology
Lacrimal gland specimens from patients with dry eye show prominent fibrosis, increase in CD4 stromal fibroblasts in the glandular interstitium and infiltration of T cells in to the periductal areas. Periductal fibroblasts are involved in the fibrogenic and immune processes by interacting with T cells in the lacrimal gland of patients with chronic GVHD resulting in rapidly progressive dry eye.

Activated fibroblasts synthesize an excess amount of extracellular matrix resulting in rapid interstitial fibrosis. On the other hand CD8 lymphocytes which are activated through antigen recognition and the helper function aided by CD4 cells infiltrate and destroy the duct epithelium. Multilayered basal lamina of ducts, lobules and vessels is seen. This is the result of repeated damage and repair due to the immune process. The degree of thickening correlates with the severity of dry eye.

Risk factors
GVHD is the major risk factor for the development of dry eye. KCS occurred more frequently in patients with chronic GVHD than in those with acute GVHD. Dry
eye is observed in patients receiving autologous or syngenic transplants who are not at risk for GVHD implying a cause beyond a simple alloreactive immune reaction.61

As conditioning regimens, TBI administered as a single dose rather than in fractions and chemotherapy alone before BMT, both increase the risk of keratoconjunctivitis sicca.61

**Clinical Features**

Dry eye after BMT is clinically similar to Sjogren’s syndrome in that both are characterized by decreased lacrimation. Patients with GVHD have a compromised epithelium as a result of lacrimal gland hyposcretion. They may also have a lower threshold for cytotoxicity from radiation or chemotherapy. Usually patients are asymptomatic. Punctate keratitis, persistent epithelial defects, corneal keratinisation, ulceration and perforation may be seen as a sequelae of dry eye.9

**Diagnosis**

The diagnostic tests for dry eye62-65 is given in the Appendix.

**Prognosis**

In most patients KCS persists after remission of GVHD. In one study none of the patients had normal tear function in four years of follow up.4 In another study resolution of tear function occurred in 8% of affected GVHD patients.66

**Conjunctival GVHD**
In a prospective study of 162 patients who had undergone allogenic BMT, Jack and co-workers reported findings that implicated the conjunctiva and the cornea as immunologic targets in GVHD. Histological examination revealed changes similar to those seen in cutaneous GVHD, including lymphocytic migration into the basal epithelium of the conjunctiva, presence of dyskeratotic cells and even subepithelial microvesicle formation and total separation of the epithelium in more severe cases.\(^5\)

The median onset after transplantation was about 14 days after their first manifestation of acute GVHD.\(^{58}\) The degree and severity of the conjunctival disease tends to correspond with the severity of the systemic disease.

Jabs and coworkers proposed a system for the clinical staging of conjunctival and ocular surface GVHD\(^5\)

Stage I : Characterized by conjunctival hyperemia
Stage II : Conjunctival hyperemia with the additional findings of a chemotic response or serosanginous exudates
Stage III : Pseudomembranous conjunctivitis
Stage IV : Pseudomembranous conjunctivitis with epithelial sloughing

Within days of appearance of acute GVHD, hemorrhagic conjunctivitis similar to that of viral hemorrhagic conjunctivitis may be noted. This finding often occurs in patients who are morbidly ill from acute GVHD. Hemorrhagic conjunctivitis is followed by the development of purulent conjunctivitis within three to four days. Though numerous polymorphonuclear leucocytes are present bacterial, fungal and viral cultures are generally sterile. During this exudative phase, upper tarsal ulceration can be
observed. There is scarring of the conjunctiva following resolution of the inflammatory changes. In some cases, conjunctival scarring may be found in patients without exudative or ulcerative conjunctivitis. Furthermore massive filamentary keratitis and sloughing of the corneal epithelium similar to those seen in massive recurrent corneal erosion can occur in patients with acute GVHD.

Tanin and associates showed that the conjunctival epithelium in patients stricken with GVHD reflects characteristic features of acute GVHD with infiltration of mononuclear cells expressing mature killer cells markers, suggesting that the pseudomembranous conjunctivitis associated with GVHD is the result of very acute cytotoxic form of GVHD.67

Although pseudomembranous conjunctivitis is uncommon in GVHD, its presence has been considered a marker for systemic involvement and is associated with a poor prognosis.67

**Treatment of dry eye**

*Medical Management*

Preservative free artificial tears68

Methylcellulose eye drops69

Autologous serum drops70

Epidermal growth Factor71
Fibronectin\textsuperscript{72}
Retinoic Acid\textsuperscript{73}
Topical Steroids\textsuperscript{74}
Tacrolimus\textsuperscript{74}
Cyclosporine A\textsuperscript{75} can be used

Systemic immunosuppressants such as cyclosporine (CsA) can be effective for treating ocular GVHD including lacrimal gland dysfunction. However, systemic immunosuppression is not generally prescribed for patients whose sole manifestation of GVHD is ocular complications as it may negate the overall graft-vs-tumor effect and decrease the patient survival. Topical Cyclosporine A is an immunomodulator. The anti-inflammatory effect arises largely from its ability to prevent the activation of T cells and the resulting production of cytokines and other inflammatory agents. It is found to be useful in patients with severe dry eye.\textsuperscript{75} Some studies say that penetration of topical agents is not effective, therefore sustained release subconjunctival CsA implant has been developed to bypass these epithelial barriers and significantly increase the CsA concentrations in the lacrimal gland to treat aqueous tear deficiency related to GVHD. A study on efficacy of cyclosporine implant in these patients is currently underway at Bethesda in the USA.\textsuperscript{76}

Treatment of filamentary keratitis requires treatment of the underlying dry eye condition. Patients with severe symptoms frequently benefit form mucolytic agents (N-acetylcysteine).
The management of persistent epithelial defects requires in addition to maximizing dry eye therapy, application of a bandage contact lens with judicious use of topical steroids with appropriate antibiotics to protect the compromised epithelium. Surgical intervention becomes necessary in selected cases of non healing epithelium or stromal disease which does not respond adequately to the recommended regimen.

**Surgical management**

If the ocular surface involvement is severe or progressive, punctual occlusions should be considered. There is a low threshold for the use of plugs in these patients as the plugs often dislodge early because of frequent rubbing of the eyes. Heat cautery or laser punctal stenosis may be used as an alternative to achieve the desired degree of tear preservation and surface hydration. 77

Tarsorrhaphy is a safe and time tested approach in these patients. Evidence of corneal melting is an ominous sign that may require the use of tissue glue. Multilayered amniotic membrane transplantation has been used to manage corneal perforation resulting form chronic GVHD.

**Cataract**

In additional to the ocular findings associated with compromised epithelium, cataract formation is common and can occur in 83% patients with long term follow up78 Higher incidence is seen in those with GVHD probably due to use of long term
corticosteroids. The incidence of cataract is also high in patients who had undergone TBI and had used potentially cataractogenic chemotherapeutic agents such as Busulphan.\textsuperscript{79}

Multivariate analysis showed that the total dose and the duration of corticosteroid therapy were the most important risk factor. In another study the incidence of cataract was 2.3\% at 2 years, but it did not cause significant visual impairment.\textsuperscript{80} The cataract was posterior subcapsular and surgery can be safely performed in GVHD patients.\textsuperscript{9} Phacoemulsification with IOL is done with adequate preparation of the ocular surface including lubricants, punctal occlusion and topical anti inflammatory drugs.

Recurrent bilateral multifocal \textbf{chorioretinitis with pan uveitis} has also been noted. Rarely patients may also present with uveitis which is thought to be a result of direct immunogenic attack of donor lymphocytes against host histocompatibility antigens. One rare case of scleritis with choroidal detachment as the initial clinical manifestation of acute GVHD on day 40 has been reported.\textsuperscript{26}

\textbf{Posterior segment complications:}

A variety of complications can occur and they include microvascular retinopathy, intraretinal and vitreous hemorrhage and infections.

CSR is an uncommon complication.
MATERIALS AND METHODS

Study design:

Descriptive, observational study
Study population:
Patients with aplastic anemia and various hematological malignancies that required SCT

Inclusion criteria:
Patients who had undergone bone marrow or peripheral blood stem cell transplant.

Data collection:
The principal investigator evaluated the patients for any ophthalmological complications
The information was entered in the proforma.

Methodology:
The patients who had undergone SCT had a complete ophthalmological examination.

Vision: Best Corrected visual acuity using Snellens chart and refraction.

Lids: Examined for

- Acute dermatitis/erythema with rash/ generalized erythroderma with blisters/desquamation
- Chronic dermatitis diagnosed if there is ectropion/
- lagophthalmos/scarring

In the available literature, there is controversy regarding the criteria for diagnosis of dry eyes based on clinical diagnostic tests. There is no gold standard for the diagnosis of dry eye. A number of diagnostic tests have been described in the literature for evaluation of dry eyes. All clinical tests have limited diagnostic value if performed
individually or in the absence of severe symptoms. It is not uncommon to find an abnormality of a single tear function test. Thus for diagnosis of dry eyes more than one test should be abnormal.

**Dry eye:**

The tests done for the detection of dry eye were

Schirmer’s test with paracaine 0.5% < 6mm at 5 minutes,

Debris in tear lake TBUT < 10 seconds and presence of thinning /

pannus / filaments / ulcers .

Definitions of the area and density grades of superficial punctate keratopathy on fluorescein staining

**Area (total sum of the affected area)**

A0: no punctate staining

A1: area occupies less than one third of the cornea
A2: area occupies one third to two thirds of the cornea

A3: area occupies more than two thirds of the cornea

**Density**

D0: no punctate staining

D1: sparse density

D2: moderate density

D3: high density and lesions overlap

**Criteria for diagnosis of dry eye** (At least 2/4 of the following criteria present)

1. Tear lake < 0.2mm / Tear debris

2. Tear Break Up Time < 10 seconds

3. Superficial punctate keratitis

4. Schirmer’s test 1b

**Upper tarsal Conjunctiva:**

Examined for signs of GVHD – Hyperemia / chemosis / pseudomembrane / epithelial loss and scaring.

**Uveitis:** Diagnosed by presence of cells and flare in anterior chamber and / or vitreous

**Pupils:** Pupillary reflexes and presence of relative afferent pupillary defect
IOP: Measured by Goldmann’s applanation tonometer

Cataracts: Diagnosed by slit lamp examinations after dilatation with 1% tropicamide

Grading

Classified according to the Japanese Co operative Cataract Epidemiology Study Group System

Nuclear colour
I Pale yellow
II Yellow
III Yellowish brown
IV Brown/ black

Posterior subcapsular cataract
I Opacity < normal pupil
II < moderate size pupil
III opacity > moderate sized pupil

Dilated fundus: Examination with a 20D and 90D at slit lamp

Disc: Examined for Glaucoma
CDR>0 .7, Neuroretinal rim and
Nerve fibre layer defect, oedema, margins and SVP

**BMT Retinopathy:** Cotton wool spots, telangiectasia, microaneurysm, macular edema, hard exudates, hemorrhages.

**Infections:** CMV retinitis, herpes zoster retinitis, fungus retinitis, Toxoplasmosis and endophthalmitis.

**Hematological complications:** Vitreous hemorrhage and intraretinal hemorrhage.

All patient included in this study would have undergone BMT according to the standard protocols used in Christian Medical College & Hospital, Vellore. The preparative marrow ablative regimens were standardized according to the pre transplantation diagnosis.

In general the pre BMT conditioning for

Acute Myeloid Leukaemia (AML) and Chronic Myelod Leukaemia (CML)

- Intravenous IV Busulphan 16mg per kg total dose over 4 days plus
- IV Cyclophosphamide 120mg per kg over 2 days.

Acute Lymphoid Leukaemia(ALL)

- IV Cyclophosphamide 120mg per kg over 2 days plus
- Total body irradiation 12 Gray over 3 days (2 Gray twice a day with linear accelerator)

Aplastic anemia

- IV Fludarabine 180mg per msq over 6 days plus
- IV Cyclophosphamide 120mg per kg over 2 days +/-
- Antithymocyte globulin 10mg per kg per day for 4 days.

Thalassemia

- IV Busulphan 16mg per kg total dose over 4 days plus
- IV Cyclophosphamide 120mg per kg over 4 days and
- Antithymocyte globulin 10mg per kg per day for 4 days

TBI is given in acute lymphocytic leukemia and if there is CNS involvement.

GVHD prophylaxis

* Cyclosporine* IV 5mg per kg per day in divided doses for 3 to 6 months in leukemia and for one year in thalassemia and aplastic anemia plus

* Methotrexate* 10mg per metre sq per day on day 1 and 7mg per metre sq per day on days 3, 6 and 11.

*IV Methylprednisolone* 1mg per kg per day tapered over one month if the patient had jaundice.

GVHD staging
Skin GVHD graded according to the extent of involvement of the total body surface area. Clinical staging of liver disease is based on the elevation of the liver enzyme and the bilirubin levels while staging of the gastrointestinal involvement is based on the volume of diarrhea.

**Data Analysis**: Data entry was done using SPSS version. Statistical analysis was done using a Statistical Package STATA.

**Statistical Methods**

Statistical Methods employed in the study was the Chi Square Test to test the association between

Dry eye and GVHD

Systemic infections and ocular morbidity

Dry eye in bone marrow compared to peripheral blood stem cell transplant

Conjunctival GVHD in bone marrow compared to peripheral blood stem cell transplant.

**Results**

A total of 40 patients who had undergone bone marrow and peripheral blood stem cell transplantation were studied. The majority were males. The mean age was 24.3 years (SD 12.4). The age range was from 5 to 51 years.

Age wise grouping of patients who underwent transplantation is shown in the following table
### Table showing age wise distribution of patients: Table 1

<table>
<thead>
<tr>
<th>Age group</th>
<th>Number of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 years</td>
<td>7</td>
<td>17.5%</td>
</tr>
<tr>
<td>11 - 20 years</td>
<td>7</td>
<td>17.5%</td>
</tr>
<tr>
<td>21 - 30 years</td>
<td>12</td>
<td>30%</td>
</tr>
<tr>
<td>31 - 40 years</td>
<td>10</td>
<td>25%</td>
</tr>
<tr>
<td>41 - 50 years</td>
<td>3</td>
<td>7.5%</td>
</tr>
<tr>
<td>&gt; 51 years</td>
<td>1</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

In our study the majority of patients who underwent transplantation were below 30 years of age.

### Transplant details

**Indications:**

Leukemias were the commonest indications for transplantation (table 2)

The other indications were aplastic anaemia, thalassemia and myelodysplastic syndromes.

### Table showing distribution of indications for bone marrow transplantation: Table 2

<table>
<thead>
<tr>
<th>Indication for BMT</th>
<th>Number of</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th></th>
<th>patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>21</td>
<td>52.5%</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>6</td>
<td>15%</td>
</tr>
<tr>
<td>Thalassemia</td>
<td>6</td>
<td>15%</td>
</tr>
<tr>
<td>Myelo dysplastic syndrome</td>
<td>2</td>
<td>5%</td>
</tr>
<tr>
<td>Others *</td>
<td>5</td>
<td>12.5%</td>
</tr>
</tbody>
</table>

- **Others**: Paroxysmal Nocturnal Haemoglobinuria, High grade peripheral T cell lymphoma, Blackfan Diamond syndrome, Granulocytic sarcoma, Dyskeratosis congenita.

**Types of bone marrow transplantation:**

39/40 (97.5%) of the patients studied had allogenic transplantation. Only 1/40 (2.5%) had autologous transplantation. Majority 25/40 (62.5%) had Allogenic / PBSC/HLA matched transplantation.

**Table showing distribution of types of transplants :**Table 3
<table>
<thead>
<tr>
<th>Type of transplantation</th>
<th>Number of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allogenic / PBSC/HLA Matched</td>
<td>25</td>
<td>62.5%</td>
</tr>
<tr>
<td>Allogenic / BMT/HLA Matched</td>
<td>13</td>
<td>32.5%</td>
</tr>
<tr>
<td>Autologous /PBSC/ HLA Matched</td>
<td>1</td>
<td>2.5%</td>
</tr>
<tr>
<td>Allogenic cord blood HLA Matched</td>
<td>1</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

**Conditioning:**

For conditioning prior to BMT 31/40 (77.5%) received chemotherapy and the remaining 9 (22.5%) received both, total body irradiation and chemotherapy. These were based on standard protocols for each disease.

**Table showing distribution of conditioning regimen: Table 4**

<table>
<thead>
<tr>
<th>Conditioning</th>
<th>No of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy alone</td>
<td>31</td>
<td>77%</td>
</tr>
<tr>
<td>Chemotherapy &amp; Total body irradiation</td>
<td>9</td>
<td>23%</td>
</tr>
</tbody>
</table>

**Engraftment**

The mean engraftment time was 19 days (SD 10.5). The range was from 10 days to 69 days.
Table showing distribution of engraftment time: Table 5

<table>
<thead>
<tr>
<th>Engraftment time</th>
<th>Number of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 days</td>
<td>1</td>
<td>2.5%</td>
</tr>
<tr>
<td>10 to 20 days</td>
<td>26</td>
<td>65%</td>
</tr>
<tr>
<td>21 to 30 days</td>
<td>10</td>
<td>25%</td>
</tr>
<tr>
<td>31 to 40 days</td>
<td>1</td>
<td>2.5%</td>
</tr>
<tr>
<td>&gt; 40 days</td>
<td>2</td>
<td>5%</td>
</tr>
</tbody>
</table>

Infections

50% of the patients studied had systemic infection post BMT. Bacterial sepsis was the commonest, seen in 11/40 (27.5%) patients. 8/40 (20%) of patients had multiple sites of infection. The remaining patients did not have any infection. None of the patients had ocular infection.

Systemic graft vs host disease

24/40 patients (60%) of patients had developed systemic graft versus host disease (GVHD). 18/40 (45%) had acute GVHD and 6/40 (15%) had chronic GVHD.

Table showing distribution of sites involved in graft versus host disease (acute and chronic): Table 6

<table>
<thead>
<tr>
<th>Sites of GVHD</th>
<th>Number of patients</th>
<th>%</th>
</tr>
</thead>
</table>
Skin was the commonest site involved in GVHD seen in 58% of the patients, followed by liver and then the gastrointestinal tract.

Table showing distribution of multiple sites involvement in graft versus host disease:

Table 7

<table>
<thead>
<tr>
<th>GVHD involving multiple sites</th>
<th>Number of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and liver</td>
<td>5</td>
<td>12.5%</td>
</tr>
<tr>
<td>Skin and GIT</td>
<td>2</td>
<td>5 %</td>
</tr>
<tr>
<td>Liver and GIT</td>
<td>3</td>
<td>7.5%</td>
</tr>
</tbody>
</table>

14 (35%) patients had GVHD involving only a single site while 10 (25%) had GVHD involving multiple organs (ie) skin, liver and GIT

**Ocular Morbidity in the post transplant period**

26/40 (65%) patients had ocular morbidity following transplantation. 18/40 (45%) of the patients had more than one type of complication in the eye.
Dry eye was the commonest ocular morbidity seen after transplantation seen in 57.5% patients. This was followed by Conjunctival GVHD in 35% of patients and 15% had cataract. The cataracts were mostly grade one posterior subcapsular cataract. Of the remaining 34 patients 2 patients were pseudophakic prior to the transplant. Pre-existing vitreous hemorrhage and refractive error was seen in 7.5% each. 5% of patients had retinal complications like cystoid macular oedema and epiretinal membrane.

Table showing distribution of patients with ocular morbidity: Table No: 8

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry eye</td>
<td>23</td>
<td>57.5%</td>
</tr>
<tr>
<td>Conjunctival GVHD</td>
<td>14</td>
<td>35%</td>
</tr>
<tr>
<td>Cataracts</td>
<td>6</td>
<td>15%</td>
</tr>
<tr>
<td>Vitreous Hemorrhage</td>
<td>3</td>
<td>7.5%</td>
</tr>
<tr>
<td>Refractive error</td>
<td>3</td>
<td>7.5%</td>
</tr>
<tr>
<td>Retinal changes</td>
<td>2</td>
<td>5%</td>
</tr>
<tr>
<td>Lid changes</td>
<td>1</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

* Retinal changes – ERM (epiretinal membrane), CME (cystoid macular edema)
16/23 (69%) of the patients with dry eye had received chemotherapy as conditioning therapy while 7/23 (31%) patients had received both chemotherapy and radiation therapy.

Only one patient had lid changes causing an ectropion. None of the patients studied had uveitis, pupillary abnormalities, raised intraocular pressures or ocular infections.

**Multiple ocular complications**

Few patients had multiple ocular complications as shown in Table 9. The most common was dry eye associated with conjunctival GVHD seen in 32.5% of patients. This was followed by dry eye with cataract seen in 7.5% of patients. One patient with vitreous hemorrhage had an associated dry eye and one patient had conjunctival GVHD with a pre-existing vitreous hemorrhage.

**Table showing distribution of multiple Ocular Complications Table No :9**

<table>
<thead>
<tr>
<th>Multiple Ocular Complications</th>
<th>No of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry eye + conj GVHD</td>
<td>13</td>
<td>32.5%</td>
</tr>
<tr>
<td>Dry eye + Cataract</td>
<td>3</td>
<td>7.5%</td>
</tr>
<tr>
<td>Dry eye + Vitreous Hemorrhage</td>
<td>1</td>
<td>2.5%</td>
</tr>
<tr>
<td>Conj GVHD + Vitreous Hemorrhage</td>
<td>1</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

**Visual Acuity**
Visual impairment. ie Best Corrected Visual Acuity (BCVA) <6/6 was seen in 37.5%. Severe dry eye was the commonest cause seen in 20%. These patients had BCVA varying from 6/36 to 6/6p. Pre-existing refractive error and vitreous hemorrhage causing decrease in vision was noted in 7.5% each. Two patients had retinal changes after the transplantation.

Table showing distribution of causes of visual impairment Table No: 10

<table>
<thead>
<tr>
<th>Causes of visual impairment</th>
<th>Total number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry eye</td>
<td>8</td>
<td>20%</td>
</tr>
<tr>
<td>Refractive error</td>
<td>3</td>
<td>7.5%</td>
</tr>
<tr>
<td>Retinal change</td>
<td>2</td>
<td>5%</td>
</tr>
<tr>
<td>Vitreous hemorrhage</td>
<td>3</td>
<td>7.5%</td>
</tr>
</tbody>
</table>

Dry eye was the commonest ocular complication seen after transplantation. Dry was also the commonest cause for visual impairment.

Table showing distribution of criteria for dry eye  Table No :11

<table>
<thead>
<tr>
<th>Dry eye criteria</th>
<th>Total 23 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tear film Break Up Time&lt;10 secs</td>
<td>23</td>
</tr>
<tr>
<td>Tear lake&lt;0.2mm\Tear Debris</td>
<td>20</td>
</tr>
<tr>
<td>Superficial Punctate Keratitis</td>
<td>15</td>
</tr>
<tr>
<td>Schirmer test I b</td>
<td>13</td>
</tr>
<tr>
<td>Filamentary keratopathy</td>
<td>3</td>
</tr>
</tbody>
</table>
All the patients with dry eye had an altered tear break up time. A decreased tear lake with or without associated tear debris was the next most common finding in dry eye followed by superficial punctate keratitis. Three patients had severe dry eye with filamentary keratopathy. None of the patients studied had corneal thinning.

All the patients with dry eye had a positive tear break up time less than 10 seconds. Of these patients more than 18/23 (78%) had at least three criteria positive for the diagnosis and 12/23 (52%) had four criteria positive for dry eye.

**Conjunctival GVHD**

Conjunctival GVHD was seen in 35% (14/40) of patients. Hyperemia was the commonest manifestation. Chemosis was not noted in any patient.

**Table showing distribution of manifestations of conjunctival GVHD**

<table>
<thead>
<tr>
<th>Conjunctival GVHD Manifestations</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperemia</td>
<td>8</td>
<td>20%</td>
</tr>
<tr>
<td>Scarring</td>
<td>5</td>
<td>12.5%</td>
</tr>
<tr>
<td>Epithelial loss and Pseudomembrane</td>
<td>1</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

Of the 14 patients who had conjunctival GVHD, 10 (75%) of them had an associated systemic GVHD.
**Table showing distribution of interventions: Table No 13**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lubricants</td>
<td>17</td>
<td>42.5%</td>
</tr>
<tr>
<td>Lubricants + steroids</td>
<td>3</td>
<td>7.5%</td>
</tr>
<tr>
<td>Lubricants + Punctal occlusions</td>
<td>2</td>
<td>5%</td>
</tr>
<tr>
<td>Lubricants + cyclosporine</td>
<td>1</td>
<td>2.5%</td>
</tr>
<tr>
<td>Vitrectomy</td>
<td>1</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

Most of the interventions were related to the treatment of dry eye. All the patients with dry eye were given lubricants. Three patients were given topical steroids in addition and two required punctal occlusion. One patient was started on Cyclosporine drops. One patient required a vitrectomy for a preexisting vitreous hemorrhage.

**Associations:**

The following associations were found on analysis:

1. Increased occurrence of dry eye in patients who had developed systemic GVHD (p Value = 0.03)
2. Increased ocular morbidity in patients with post transplant infections (p value = 0.002).
3. Same risk of developing dry with BMT and PBSCT (p value = 0.45)
4. Same risk of developing conjunctival GVHD with BMT and PBSCT (p Value 0.57)
Table showing association between systemic GVHD and dry eye - Table no: 14

<table>
<thead>
<tr>
<th>GVHD</th>
<th>Dry eye</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>17</td>
<td>7</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>6</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>17</td>
<td></td>
<td>40</td>
</tr>
</tbody>
</table>

Chi square value = 4.36
P Value = 0.03
74% (17/23) of the patients who had dry eye had GVHD. And 70% (17/24) of the patients who had GVHD had dry eye. This association was found to be significant (P value = 0.03)

Association between ocular morbidity and Systemic infections

Table showing association between ocular morbidity and systemic infections

2Table no: 15
Of the 26 patients who had ocular morbidity, 15 patients (57%) had infection in the post transplant period. Of the 20 patients who had infection in the post transplant period, 15 (75%) had developed some ocular morbidity. This association was significant $p$ value = 0.002.

### Association between dry eye in BMT vs PBSCT

Table showing association between dry eye in BMT vs PBSCT - Table 16
Dry eye was seen in 7/14 (50%) of the patients who had undergone bone marrow transplantation. In those who had PBSCT dry was seen in 15/24 (62.5%). The difference between these two groups was not significant \( P = 0.45 \)

Association between conjunctival GVHD in BMT vs PBSCT

Table showing association between conjunctival GVHD in BMT vs PBSCT

Table 17
Conjunctival GVHD was seen in 4/13 (30.7%) patients who had undergone bone marrow transplantation while this was seen in 10/25 (40%) patients who had undergone PBSCT. The difference between these two groups was not significant, p Value 0.57

**DISCUSSION**
Bone marrow and peripheral blood stem cell transplantation is a life saving procedure for an increasing number of patients. With the advent of immunology, histocompatibility testing, immunosuppressive therapy and good supportive care the pool of suitable donor marrow expands from autologous grafts to include HLA matched related individuals and fully / partially matched unrelated individuals. This increases the chance of more patients benefiting from SCT. This will result in an increased number of long-term survivors who will need specialised monitoring and management for the various post transplant complications and morbidity.

We studied 40 patients in the post transplant period who had BMT or PBSCT done in our hospital. Ocular morbidity was seen in 65% of them. These morbidity could be broadly classified as Ocular surface diseases – dry eye(57.5%), conjunctival GVHD(35%), cataracts(15%) and retinal changes( 5%).

As conditioning regimen prior to transplantation 77% received chemotherapy alone and the rest 23% had both radiation and chemotherapy. Sullivan had shown a higher incidence of dry eye in patients receiving radiotherapy in addition to chemotherapy for conditioning. In our study 77% of the patients who had received radiation prior to the transplant had developed dry eye while this was seen in 53% who had received only chemotherapy. But the number of patients who received chemotherapy and radiation were only nine compared to 31 who had only chemotherapy and hence an association could not be established.
In our study population 97% had allogenic transplants (allogenic PBSCT in 62.5% and allogenic BMT in 32.5%). Lawrence et al have shown that allogenic PBSCT has an increased incidence of systemic GVHD.\textsuperscript{4} Ocular morbidity like dry eye and conjunctival GVHD is seen more in patients with systemic GVHD.\textsuperscript{26} However we could not find a statistically significant difference in the incidence of either dry eye or conjunctival GVHD in patients who had allogenic PBSCT vs allogenic BMT in our study. (p values 0.45 and 0.57 respectively.)

**Ocular surface disease** is the most prevalent problem after haematopoietic stem cell transplantation. Of the 65% (26/40) of patients with ocular morbidity, the majority of them i.e 57% (23/40) were noted to have findings suggestive of dry eye. Jack and Hicks have noted dry eye syndrome in 40 out of 90 patients. However they have not mentioned how many of their patients had developed GVHD.\textsuperscript{82} In another study by Kenyon et al the incidence of dry eye was as high as 60% in patients with GVHD.\textsuperscript{68} This developed three months after BMT and included dry eye with corneal sequelae causing punctate keratitis, persistent epithelial defect, and sterile/infectious stromal ulceration. This illustrates the fact that dry eye is more often seen in patients with chronic GVHD and that the severity of dry eye is also more when the patient has GVHD.

The age of the patients ranged from 5 to 51 years. Of the seven patients less than 10 years of age, only one of them had dry eye. This is in keeping with a study which proved that the prevalence of dry eye syndrome is less in children than in adults owing to
healthier and faster regeneration of epithelial cells.\textsuperscript{3} However the number of children in our study was too small to establish a statistical significance.

None of the patients developed persistent epithelial defect, sterile or infectious stromal ulceration. Most of the patients as in other studies responded to topical ocular lubricants. Out of 40, three required topical steroids and two required punctal occlusion. Only one patient was given topical cyclosporine. The long term efficacy of cyclosporine drops in treatment of dry eye in GVHD has to be evaluated on follow up.

None of the patients required a major surgical intervention like Tarrsoraphy, conjunctival homograft, amniotic membrane transplantation or penetrating keratoplasty.

In this study there was a \textit{significant association} between development of \textit{dry eye} and \textit{presence of GVHD} (p value 0.03). This finding has been reported in other studies.\textsuperscript{4} Our study also showed a \textit{significant association} between \textit{ocular morbidity} and \textit{systemic infections} in the immediate post transplant period. However the exact reason for this could not be ascertained. Literature search did not reveal an increased incidence of ocular morbidity in the presence of systemic infections in other studies.

\textbf{Conjunctival GVHD}

Conjunctival GVHD is a marker for severe systemic GVHD and development of higher stage of ocular GVHD was found to be significantly associated with more severe
forms of both acute and chronic systemic GVHD. In this study of the 14 patients who had conjunctival GVHD, 10 (75%) of them had an associated systemic GVHD.

Jabs et al have reported the incidence of conjunctival GVHD to be 12% in acute GVHD and 11.1% in chronic GVHD. In the above study, most patients presented with pseudomembrane - grade 3 conjunctival GVHD. This is in contrast to our study where conjunctival GVHD was seen in 35% patients and the commonest finding was hyperemia of the conjunctiva - grade 1 conjunctival GVHD. Only one patient had a pseudomembrane formation which is a higher grade of conjunctival GVHD.

Cataract

Cataract formation is common in allogenic stem cell transplant patients occurring in as many as 83% with long term follow up. There is an association between cataract and GVHD which is said to be due to the use of long term corticosteroids. In addition pre transplant TBI conditioning is also associated with higher incidence of cataract.

Cataract was noted in 15% of our patients and all of them had grade 1 posterior subcapsular cataract. As we had not seen the patients prior to transplantation we could not attribute the cataract to transplantation. Two patients were pseudophakic prior to the transplant.

Cataract surgery with intraocular lens implantation can be safely performed in GVHD patients. Preoperative ocular surface rehabilitation, including lubricants, punctal
occlusion and topical anti-inflammatory agents is essential to reduce the incidence of complications after the surgery.

**Posterior segment complications**

Incidence of posterior segment complications post haematopoietic stem cell transplantation has been reported to be around 12%. These complications although rare, can have significant visual consequences and implications. In our study only 2 of the patients (5%) developed posterior segment complications. One had **cystoid macular edema** and the other had **epiretinal membrane**. Cystoid macular oedema has not been described in the literature in post transplant recipients. None of the patients developed BMT retinopathy/ retinal infections or optic disc oedema.

Three patients had pre existing vitreous hemorrhage prior to SCT. This could be secondary to the disease or thrombocytopenia occurring after chemotherapy.

**Miscellaneous Findings**

The cutaneous manifestations of GVHD can affect the eyelids. Dermatitis, lagophthalmos, ectropion, poliosis, madarosis, vitiligo can occur. Only one of our patients developed an **ectropion**. This was secondary to the skin GVHD that the patient had.
The first and major limitation of our study was that it involved only a subset of patients who were well enough or were willing to come for an ophthalmic evaluation and hence did not include all the patients who had come for a review post transplant. Therefore the profile of ocular morbidity described may not be accurate.

We do not know the pre BMT status of the patient. This is important because the conditions requiring transplantation such as leukaemias and anaemias by themselves are associated with significant ocular morbidity due to the associated anaemia, thrombocytopenia and polycythaemia.

The acute ocular complications could not be ascertained because the patients were not evaluated in the immediate post transplant period. This was due to the fact that they were under barrier nursing or they were acutely ill to undergo a thorough ophthalmologic evaluation.

CONCLUSION
• 65% of the patients post bone marrow and peripheral blood stem cell transplantation had ocular morbidity.

• Dry eye (57.5%) was the commonest finding followed by conjunctival GVHD (35%) and posterior subcapsular cataract (15%).

• Increased incidence of ocular morbidity is seen in patients with post transplant infections.

• Increased occurrence of dry eye is seen in patients who had developed systemic GVHD.

• The risk of developing dry eye is the same in patients who have had BMT and in those who had PBSCT.

• The risk of developing conjunctival GVHD is the same in patients who have had BMT and in those who had PBSCT.

Regular ophthalmic examination is therefore essential especially for patients who have had systemic infections and or systemic graft versus host disease for early detection and treatment of the potential complications.

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APPENDIX
APPENDIX

The diagnostic tests for dry eye are the Schirmer test, Tear break up time, Tear meniscus height and tear debris and Fluorescein staining of the cornea.

(1) Schirmer test: Measures the quantity of the tears produced by the eye.\textsuperscript{62}

**Schirmer Ia:** Tests basic and reflex secretions.

A standardized strip of filter paper (Whatman No:41) is placed in the eye. The patient is instructed to look forward and to blink normally during the course of the test. After 5 minutes the filter paper is removed and the length of the moistened part is measured. Less than 5mm of wetting is suggestive of dry eye.

**Schirmer Ib :**

The same test is done after instilling local anesthetic. This measures mainly the basal secretion. The reflex secretion is not completely abolished by this test. Less than 5mm at 5 minutes is suggestive of dry eye.

(2) Tear break up time

A drop of fluorescein is instilled in the eye, time in seconds between the last blink and the first randomly distributed dry spot is noted under slit lamp with cobalt blue illumination.\textsuperscript{63} Ten seconds is the normal cutoff for TBUT.
It is a specific test for mucin deficiency. Limitations are that erratic results occur in the absence of standard conditions and corneal surface irregularities affect accurate measurements.

(3) **Fluorescein staining of the cornea.**

Fluorescein staining manifests where cell to cell junctions are disrupted. It lacks the ability to be blocked by tear constituents and diffuses rapidly into the stroma. It acts as a vital stain adhering to devitalized cells. The area and density of staining is measured and graded.

(4) **Tear meniscus:**

Height of less than 0.2mm / presence of debris is suggestive of dry eye. Various studies have taken one or more of the above tests to diagnose dry eye.
## Proforma

Ocular complications in Bone marrow and peripheral blood stem cell transplantation

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OPHTHALMIC EVALUATION

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**Visual acuity**
- Unaided
- BCVA
- Ref error

**Lids Acute Dermatitis**
- Erythema
- Blisters
- Desquamation

**Chronic Dermatitis**
- Ectropion
- Lagophthalmos
- Scarring

**Dry eye**
- Tear lake
- Schirmer test
- TBUT

- SPK A/D
- Thinning
- Pannus
- Filaments
- Ulcer infectious / sterile

**Upper Tarsal Conjunctiva**
- Hypermia
- Chemosis
- Pseudomembrane
- Epithelial loss
- Scarring

**Uveitis**
- Anterior
Posterior
Pupil
Pan
RAPD
IOP

Cataract
NS I/II/III/IV
PSC I/II/III

BMT
Retinopathy

infections
CMV
HZ
Fungal
Toxo
Endophthalmitis

Hematologic
VH
IR Hg

CSR
ERM

Others

Intervention
Nil
Lubricants
Cyclosporine
Punctual occlusion
Tarsoraphy
Others

Examiner’s notes:

Ophthalmological diagnosis: