Study Protocol

Title: Ocular Graft-Versus-Host-Disease Following Allogeneic Haematopoietic Stem Cell Transplantation: a Territory-wide Prospective Cohort

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Background

Allogeneic haematopoietic stem cell transplantation (HSCT) is an effective treatment for all array of haematological disorders. Graft-versus-host-disease (GVHD) occurs as a result of an overactive systemic immunological response against normal host tissues, in particular the liver, skin, mucosal surface of the eye, gastrointestinal tract and genitalia.

Ocular graft-versus-host-disease (oGVHD) occurs in 30-70% patients after allogeneic HSCT [1][2]. It mainly affects the ocular surface, and pathologically it is characterized by decreased conjunctival goblet cell density, increased conjunctival squamous metaplasia and infiltration of tissues with inflammatory cells [3]. Common clinical manifestations include keratoconjunctivitis sicca, marginal keratitis, conjunctivitis and conjunctival scarring, and anterior uveitis [4]. In severe cases, these can lead to painful non-healing corneal ulcers, secondary infections and visual loss. Risk factors for oGVHD reported in the literature included non-Caucasian race, male recipient from female donor, more extensive and severe systemic involvement, pre-existing diabetes mellitus and use of anti-thymocyte globulin [5][6][7][8].

oGVHD can be debilitating and severely impact patients' quality of life. Although common and significant, currently there are no widely accepted guidelines available for prophylaxis and management.

The Haemopoietic Stem Cell Transplantation Centre at Queen Mary Hospital is the only quaternary referral centre for adults in Hong Kong since 1990 and now it serves over 100 patients per year [9]. In collaboration with the Department of Haematology of QMH, we set out to establish a territory-wide cohort of patients receiving allogeneic HSCT to fill the current knowledge gaps.

References

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Objectives

1. To establish the population-based epidemiology of oGVHD after allogeneic HSCT
2. To understand the natural history and long-term ophthalmic outcomes in chronic oGVHD
3. To perform quantitative analysis of ocular surface changes in oGVHD
4. To identify biomarkers in blood and tear samples in oGVHD
5. To investigate the change in the ophthalmic microbiome in oGVHD over time
6. To recruit patients for future clinical trials on prophylactic and therapeutic regiments

Plan of Investigation:

Study Design

We proposed a prospective cohort study with up to five years of follow-up. Enrolled patients will be seen at baseline before HSCT, and at months 3, 6, 9, 12; and optional at months 18, 24 and annually up to 5 years.

The following examinations will be performed at some of the visits where appropriate:

(1) Clinical examination

This includes visual acuity, intraocular pressure, slit-lamp and fundus examination.

(2) Tear assessment

This includes tear breakup time (TBUT), fluorescein staining pattern, Schirmer's test (no anaesthetics), tear osmolarity and tear matrix metalloproteinase-9 (MMP-9).

(3) Ocular surface imaging

Meibography and quantitative tear film parameters by Keratography 5M and LipiView, pachymetry, specular microscopy and pentacam will be used.

(4) Fundus imaging

Optical coherence tomography (OCT) of the retinal nerve fibre layer (RNFL) and

macula will be taken. Fundus structure will be captured by a wide-field fundus camera.

(5) Questionnaires

Several dry eye questionnaires for symptom severity and burden on quality of life will be administered

(6) Collection of a tear sample

Tear from the conjunctival sac will be collected by the following tools:

i. InflammaDry® test kit (Quidel, San Diego, California, USA)
ii. TearLab™ Osmolarity System (TearLab Corp., Escondido, California, USA)
iii. Capillary glass tube
iv. Schirmer's test paper

(7) Collection of conjunctival swabs

Conjunctival samples will be collected by using swabs for laboratory investigation of the ocular microbiome.

(8) Collection of a blood sample

Blood samples will be collected during regular blood taking at the Department of Haematology, Queen Mary Hospital.

Subjects

In a two-year recruitment period, all patients attending the pre-HSCT assessment clinic in the Bone Marrow Transplant Centre (BMTC) at Queen Mary Hospital (QMH) will be invited to join the cohort. The sample size is estimated to be 250. This is based on the calculation that, each year, approximately 120-130 patients underwent allogeneic HSCT at the BMTC of QMH.

Inclusion Criteria

- Patient aged 18 or above

- Underwent allogeneic HSCT in QMH in the two-year recruitment period

Exclusion Criteria

- Underwent autologous HSCT
- Patient unable to attend follow-up visits

Family Control Subjects

The research team will invite an accompanying family member to be the family control. Microbiome and tear samples will be collected for comparison. The sample collection schedule is the same as the corresponding post-HSCT case.

Outcomes

Primary outcome:

- The population-based epidemiology, natural history and long-term ophthalmic outcomes of oGVHD after allogeneic HSCT

Secondary outcomes:

- A quantitative description of ocular surface changes in oGVHD
- The change in the ophthalmic microbiome in oGVHD over time

Data Processing and Statistics

The proportion of detectable ocular microbiome in tear samples between patients will be compared using Fisher's exact test. Factors affecting the change of ocular microbiome in oGVHD, for example age, gender, days from onset of symptoms, intraocular pressure, and central corneal thickness, will be studied using logistic and linear regression models. All statistical analyses will be performed using software packages STATA (Statacorp LLC, USA) and R (The R Foundation, Austria).

Data Handling and Record Keeping

Each participant will be assigned a study number at time of enrollment. Data collected will be stored in a password-protected computer and processed without any patient identifying number. Patient confidentiality and data security will be strictly observed in accordance with the University’s and Department data security guidelines and data

management plans. Personal data will be discarded within 5 years after the completion of the study.

Ethics

All study procedures will be explained to participants and written informed consent obtained. There are no additional interventions and particular risks induced.

Financial Interest

There is no financial or conflict of interest to declare.