

# NSW Protocol for Autologous Haematopoietic Stem Cell Transplantation for Systemic Sclerosis

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## Glossary

ACI	NSW Agency for Clinical Innovation
ANA	Antinuclear antibody
ATG	Anti-thymocyte globulin
BMT	Blood and marrow transplant
CT	Computed tomography
DLCO/VA	Diffusing capacity divided by the alveolar volume
dsDNA	Double-stranded deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
ENA	Extractable nuclear antigen antibodies
EUC	Electrolytes, urea and creatinine
HSCT	Haematopoietic stem cell transplantation
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HAQ	Health assessment questionnaire
HealthPACT	Health Policy Advisory Committee on Technology
HREC	Human Research Ethics Committee
HPV	Human papillomavirus
HDCy	High dose cyclophosphamide
ICU	Intensive care unit
LDH	Lactate dehydrogenase
LHD	Local health district
LFT	Liver function test
LV	Left ventricular
mPAP	Mean pulmonary artery pressure
MoH	NSW Ministry of Health
MRI	Medical resonance imaging
NAT	Nucleic Acid Test
PBMNC	Peripheral blood mononuclear cells
PICF	Participant information and consent form
QOL	Quality of life
SSc	Systemic sclerosis
TLC	Total lung capacity
TRM	Transplant related mortality
VAS	Visual analogue scale

## Background

There is increasing evidence for the use of autologous haematopoietic stem cell transplantation (HSCT) in severe autoimmune diseases. HSCT is used as a high dose immunosuppression, with haematopoietic stem cell rescue employed as a safe way of delivering chemotherapy with minimal periods of neutropenia. It is hypothesised that reinfused stem cells reconstitute a tolerant immune system and the chemotherapy eradicates the auto-reactive immune clone. There is in vitro evidence, as well as significant Phase II and Phase III trial data<sup>1-3</sup> to confirm that HSCT can be used in the management of patients with severe resistant autoimmune conditions. The 2015 HealthPACT report, “Stem Cell Therapy for Non-Haematological (Autoimmune) Indications”, highlights that this is especially true for patients with Systemic Sclerosis (SSc), where trial data has demonstrated autologous HSCT to be an effective treatment<sup>4</sup>.

Although acknowledged as a treatment option, St Vincent’s continue to provide the service under the auspices of a clinical trial. This provides the extra benefits of ethical and governance oversight and supports research aimed at further improving this treatment for patients.

The ACI Blood and Marrow Transplant Network has collaborated with the NSW Ministry of Health to formalise the recognition of HSCT as a treatment option and to purchase activity using the following protocol to improve health outcomes for people with systemic sclerosis.

## Purpose

To provide guidance regarding autologous haematopoietic stem cell transplantation for systemic sclerosis including:

1. Referral from consultant physician to the transplant centre
2. Patient assessment process with inclusion and exclusion criteria
3. Suggested protocol for mobilisation and transplantation
4. Follow-up.

## Protocol

### 1. Referral to NSW HSCT services for the treatment of Systemic Sclerosis

A consultant physician will diagnose patients with Systemic Sclerosis (SSc) using standardised criteria such as clinical history, examination and blood tests. Once diagnosed, a referral for HSCT must be made by a consultant physician with a specialty interest in rheumatology, immunology, or other specialties where autoimmune conditions, such as SSc occur.

Enquiries and referrals should contact the Haematology Office, Kinghorn Cancer Centre, Phone 02 9355 5656 or 02 9355 5657, Fax 02 9355 5602.

#### ***Patient assessment process***

To assess the suitability of a patient for HSCT, the following documentation and results are required:

- confirmation of diagnosis and history with an accompanying letter from a consultant physician
- high resolution CT scan of chest with pulmonary function tests
- blood workup (including full blood count, biochemistry, autoimmune serology)

- a basic assessment of cardiac function (such as a cardiac echo) is reasonable to provide at this time but a full cardiology review with right heart catheter and cardiac MRI<sup>5</sup> will be performed at St Vincent's Hospital once the referral is received, as well as apheresis consult and venous access assessment
- rheumatology review.

When patients are referred to St Vincent's Hospital they are entered into a HSCT for Autoimmune Diseases database. Each patient is assessed individually according to standard dose inclusion and exclusion criteria (see below) for their suitability to be treated with HSCT. SSc referrals for HSCT are presented at a bone marrow transplant multidisciplinary team (MDT) meeting. If accepted, patients are entered into the program at that point.

Note: When planning admissions public holidays and annual leave of senior staff should be considered.

Patients that do not meet the standard dose protocol may be eligible for a lower dose protocol (ASSURE trial) as approved by the St Vincent's Hospital Ethics Committee (Section 3). A clinical judgement based on clinical work-up (including cardiac investigations) is required to be made and documented. Patient will be offered this option at this point pending approval by their referring physician and written informed consent from the patient. The transplant will be tracked as a 'planned deviation' and the following minimum details recorded in the BMT Network Q-Pulse quality management system – opportunity for improvement (OFI) module:

- date of transplant, initials of recipient
- pre-approval by BMT Program Director
- cyclophosphamide dose used
- reason for use of low dose
- any serious adverse events
- outcome (e.g. skin scores, transplant related mortality (TRM))
- review and approval of the OFI by the BMT Program Medical Director.

## **2. Standard Dose: Inclusion and exclusion criteria for the HSCT**

### *Inclusion criteria*

- Age 18-65
- Adequate organ function as measured by:
- Cardiac LV Ejection Fraction >45%
- Total Lung Capacity ≥60%
- Resting mean pulmonary artery pressure (mPAP) <25mmHg
- mPAP <30mm/hg after 500mls bolus

- DLCO/VA<sup>i</sup> ≥50%
- Adequate Cardiac MRI with absence of diastolic septal flattening
- ECOG<sup>ii</sup> 0,1 or 2
- Negative serology and NAT for HBV, HCV and HIV
- Negative pregnancy test
- Absence of severe chronic infection
- Severe auto-immune disease (ideally <7 years duration) unresponsive to multiple standard therapies including corticosteroids
- Sperm collection or ova cryopreservation is to be offered prior to HSCT in those of child-bearing age
- Early, rapidly progressive inflammatory diffuse SSc with truncal skin involvement and/or involving lungs which has failed to stabilise with standard anti-rheumatic agents. All patients with severe SSc will undergo right heart catheterisation prior to cyclophosphamide mobilisation to assess for pulmonary artery pressure under fluid challenge (as per above). Ideally patients will also have signs of ongoing disease-related inflammation immediately prior to HSCT. Early disease is defined as disease in which the timing from second symptom onset to HSCT is seven years or less
- Patient work-up as for any patient undergoing autologous stem cell mobilisation, collection and transplant requires: completion of donor questionnaire; consent for storage and disposal of cells; consent for chemotherapy; consent for vascath; consent for apheresis; consent for blood product transfusion; consent for central line insertion and consent for transplant. Patients are also required to sign the HREC PICF.

#### Exclusion criteria

- ECOG 3 or 4
- Untreated or uncontrolled heart failure, arrhythmia or ischaemic heart disease
- Prior history of malignancy or other current medical condition which in the opinion of the investigators would restrict the ability of the patient to tolerate the procedure
- Unable to provide informed consent and/or the diagnosis of mental or cognitive deficits which could interfere with the capability of providing informed consent
- Major bone marrow failure such as significant neutropenia (<1000/uL) or thrombocytopenia (<100,000/uL)
- Severe renal or liver disease.

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<sup>i</sup> Diffusing capacity divided by the alveolar volume

<sup>ii</sup> ECOG is a function status and performance scoring tool

### **3. ASSURE trial: Inclusion and exclusion criteria for the lower dose cyclophosphamide protocol**

#### *Inclusion criteria*

- Able to provide informed written consent
- Severe SSc either de novo or unresponsive to previous therapies requiring HSCT (in the opinion of the referring physician)
- Age 16-65
- ECOG 0,1,2,3
- Negative serology and NAT for HIV
- If hepatitis B +ve – willing to take entacavir for one year
- If hepatitis C +ve – must be cleared by anti-viral therapy prior to HSCT
- Negative pregnancy test
- Absence of severe chronic infection
- Sperm collection or ova cryopreservation is to be offered prior to HSCT in those of childbearing age
- Ineligible for HDCy using 200mg/kg due to pre-existing cardio-respiratory disease.

#### *Exclusion criteria*

- Karnofsky 40% or less
- Cardiac Ejection fraction <40%
- mPAP >50mmHg
- DLCO/VA <30%
- Unstable coronary artery disease
- Prior history of malignancy or other current medical condition which in the opinion of the investigators would restrict the ability of the patient to tolerate the procedure
- Unable to provide informed consent and/or the diagnosis of mental and cognitive deficits which can interfere with the capability of providing the informed consent
- Major bone marrow failure or condition which results in significant neutropenia (<1000/uL) or thrombocytopenia (<100,000/uL)
- Severe renal (serum creatinine >200µmol/L) or liver disease (Bilirubin >50µmol/L or known cirrhosis)
- Uncontrolled infection.

## 4. Suggested protocol for mobilisation and transplantation

### ***Mobilisation of peripheral blood stem cells***

- Patients will undergo stem cell collection following 2g/m<sup>2</sup> (Low dose ASSURE trial 1g/m<sup>2</sup>) cyclophosphamide after informed written consent.
- Intravenous fluids will be prescribed to run concurrently with cyclophosphamide as described:
  - Standard Dose: 1L over two hours pre-cyclophosphamide followed by 1L every 4 hours.
  - ASSURE: 1L over two hours pre-cyclophosphamide followed by 1L every 12 hours which is reviewed according to fluid balance, or change in patient's clinical condition.

Note: Fluids may vary from patient to patient especially when they have cardiac disease. Patients should be weighed twice daily, urine output, urinalysis and B/P monitored to guide IV fluid ordering.

- The following day, patients will be discharged home from the ward and daily GCSF 10mcg/kg for 10 -12 days will be administered until the following week when a peripheral blood CD34+ count will be performed.
- If the CD34+ count is >10/uL, then patients will undergo leukapheresis to obtain a minimum CD34 collection target of 2 x 10<sup>6</sup>/kg. CD34+ haematopoietic stem cells will then be cryopreserved as per standard operating procedures. Patients are likely to require vascath insertion on the day prior to leukapheresis if venous access is not adequate – this would require a second consent form as per standard practice.

### ***HSCT procedure***

Within 4-8 weeks of stem cell collection and cryopreservation the patients are to be admitted for the HSCT procedure.

- Patients will be placed in a single room and chemo-immunotherapy will be administered via a central venous line placed on D-7.
- ASSURE patients will be in cardiac monitoring with daily Troponin, ProBNP and cardiac review at least until 24 hours post cyclophosphamide and if cleared by the cardiology team.
- Standard Dose: Cyclophosphamide 50mg/kg for 4 days (Standard dose with hyperhydration + Mesna).
- ASSURE trial: Cyclophosphamide 12.5-35mg/kg with mesna + IVF as per patient's clinical status and a minimum of twice daily review of their weight.
- Anti-thymocyte globulin (ATG – Horse, ATGAM) 10mg/kg will be administered for 4 days after a test dose is administered on D-6.
- Methylprednisolone 1mg/kg will be given as serum sickness prophylaxis on the days of ATG.
- A minimum of 2 x 10<sup>6</sup>/kg CD34+ cells without manipulation will be infused on Day 0.
- All patients will receive standard intravenous antibiotics upon neutropenic fever after blood cultures and chest x-ray.

- In order to prevent hypertensive crisis, all SSc patients will receive antihypertensive (e.g. captopril) if they have not been on any previously to a maximally tolerated dose to maintain systolic blood pressure at 100 systolic.
- Following engraftment, all patients will receive bactrim 1600mg/800mg, fluconazole and valaciclovir for prophylaxis of pneumocystitis jejun, candida albicans and herpes zoster respectively for six months.

## 5. Follow up visits and assessment

All patients will have standardised follow up visits at the transplant unit performed at 3, 6, 12 and 24 months and subsequently yearly in order to assess long-term safety, efficacy and possible relapse of disease. During this visit and pre-HSCT, all patients will have specific monitoring of their disease using disease-specific questionnaires and quality of life assessments.

- All patients will have a full blood count and C-reactive protein, biochemistry (EUC, LFT, LDH) and immunology tests (ANA, dsDNA, ENA) performed as per standard of care at each of these visits.
- At the same venepuncture as these standard blood tests, patients will have two extra EDTA (normal FBC tubes) collected for peripheral blood mononuclear cells (PBMNC) which will be stored at –80 degrees Celsius for future immune reconstitution studies (for assessment of CD4, 8, 19, Naïve T cells and T regulatory Cells post HSCT).
- All patients will have a six minute walk test performed pre HSCT and at 12 months post HSCT.
- The modified Rodnan Skin Score will be performed on all patients pre-mobilisation and at 3, 6, 12 and 24 months and subsequently yearly.
- The patients will complete a case report form containing a visual analogue scale (VAS) for pain and disease, a health assessment questionnaire (HAQ) and the SF36 QOL questionnaire.
- Lung function tests will be performed yearly post-HSCT for the Standard dose and 3, 6, 12 monthly and yearly thereafter for ASSURE trial.

## Trial status

If the trial is prematurely terminated or suspended for any reason, the Clinical Lead or delegate should promptly inform the SVH HREC, and assure appropriate therapy and patient follow-up. Patients who are scheduled for HSCT will be informed of the status of the trial. The ACI and MoH should also be notified in a timely fashion including reason for the suspension.

## Evaluation review meeting

The Evaluation Governance Group will meet every six months to review safety, outcomes and delivery. The group will be made up at a minimum of the St Vincent's Clinical Lead and representative members of ACI, MoH, St Vincent's Executive and the St Vincent's Haematology Department.

A report will be tabled detailing:

- number of patients transplanted and on which protocol (standard vs low dose cyclophosphamide)
- number of patients enrolled for the next six months
- number of patients treated off-protocol and reason
- referred patients not proceeding to transplant
- post code of patients
- current status of all patients transplanted
- admissions to ICU, readmission to hospital or death
- 100 day TRM in both standard and low dose cohorts
- patient experience outcomes (ACI to assist)
- challenges in meeting allocated volumes (e.g. ward closures)
- current staffing levels
- any changes to the protocol.

An evaluation of the systemic sclerosis service is being conducted by the BMT Network for the NSW Health Ministry Health System Planning and Investment Branch looking at the equity of access for NSW patients, patient experience and transplant outcome. The report will be completed in 2019.

### **Protocol review**

The *NSW Referral and Protocol for Haematopoietic Stem Cell Transplantation for Systemic Sclerosis* including inclusion and exclusion criteria will be reviewed annually by the BMT Network Council. Additional clinical advice may be sought outside of the Council at the discretion of the BMT Network council.

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