AHSCT for Systemic Sclerosis

Canada - Australia Inclusion/Exclusion Guidelines

And

Canada-Australia Interim Recommendations for Cardiac Assessment and Criteria of AHSCT Exclusion

Note: Most of the wording of the items is exactly as used in the Delphi exercise. After the Delphi results were available, there was further discussion among members of the steering committee, with other specialists such as transplant hematologists, nephrologists and gastroenterologists, and the results were presented at a meeting in Canada in April 2019 attended by Canadian rheumatologists with an interest in SSc and transplant hematologists from Canada and the United States. Based on this input after the Delphi, the "notes of caution" were added and the final document was approved by the steering committee.

INCLUSION CRITERIA

1. Age

18-70 years

AND

2. Diagnosis

Meet 2013 ACR/EULAR criteria or SSc.

AND

3. Skin and Disease Duration

3a: < 4 years since onset of skin thickening AND mRSS >30 OR mRSS> 20 and includes trunk

OR

3b. ≥4 years AND < 10 years since onset of skin thickening AND mRSS > 20 AND increase in mRSS over past year of > 7

OR

4. Interstitial Lung Disease

At any time, and irrespective of skin involvement:

- ILD with FVC < 70 or DLCO < 60% AND
- CT scan evidence of 20% of lung involved AND
- Received treatment for at least 1 year AND
- Decrease absolute FVC >10% OR decrease absolute DLCO > 15% over the most recent year of treatment

NOTE: The important concept here is that a patient may meet criteria for either skin disease **OR** lung disease.

EXCLUSION CRITERIA

1. Pregnancy

Pregnancy or unwillingness to use adequate contraception

2. Lung

Severe pulmonary dysfunction defined as:

- a hemoglobin-corrected DLCOc < 45% of predicted at the pretransplant evaluation, OR
- FVC < 45% of predicted at the pretransplant evaluation OR
- pO2 < 70 mmHg or pCO2 > 45 mmHg without supplemental oxygen

3. Renal

3a. For patients receiving 8 Gy TBI with renal and lung shielding to 2 Gy, CY 120 mg/kg + ATG conditioning: Estimated EGFR < 40 mL/min based on MDRD equation

Or

3b. For patients receiving CY 200 mg/kg + ATG conditioning: Estimated glomerular filtration rate (EGFR) < 60 mL/min/1.73m2 based on MDRD equation

OR

3c. Active or untreated SSc renal crisis at the time of pretransplant evaluation. Presence of nephrotic range proteinuria (defined as >3.5 gms/24 hours, or protein:creatinine ratio >3.5), active urinary sediment, urinary RBCs > 25 per HPF, or red cell casts require further investigation by a nephrologist to rule out glomerulonephritis, overlap syndromes, or other causes of renal disease.

Note of Caution: In the SCOT and STAT trials, patients who died had EGFR <60.

4. Malignancy

Malignancy within the 2 years prior to mobilization, excluding adequately treated squamous cell skin cancer, basal cell carcinoma, and carcinoma in situ.

Treatment must be completed (with the exception of hormonal therapy for breast cancer) with durable cure/remission status verified for at least 2 years duration prior to mobilization of PBSC.

5. Hematologic

Hematologic abnormalities, not related to the underlying disease or an autoimmune phenomenon, as defined below (as per peripheral blood counts during the pre-transplant evaluation, not attributable to transient and reversible effects of medications)

5a. Absolute neutrophil count (ANC) < 1500 cells/uL

OR

5b. Platelets < 50,000 cells/uL (as per peripheral blood counts during the pre-transplant evaluation, not attributed to transient and reversible effect of medications) OR if Platelets < 100,000 cells/uL and >50,000 cells/uL allow transplant only if transplant haematologist.

OR

5c. Hematocrit < 27% at time of transplant. This must be assessed at least 1 month after any attempt to treat and correct anemia of any cause.

Or

5d. Hemoglobin < 9.0 g/d at time of transplant. This must be the assessed at least 1 month after any attempt to treat and correct anemia of any cause.

6. Myelodysplasia

7. Liver

Screening tests : Obtain ALT, ALP & GGT , HBV / HCV in all cases. Alkaline phosphatase to look for undiagnosed Primary Biliary Cirrhosis (PBC)

ALT: define normal as follows: M < 33 iu/l, F < 25 iu/l. These may not be the normal values in all labs but these are the values that should be used.

If ALT < 3 X ULN, no further tests are required, and the patient can undergo transplant unless there is an excess alcohol intake (see below for definition).

Get fibroscan if:

a) Subject drinks > 1 glass ETOH/day (> 40 gr/d)

b) Any ALT > 3 x ULN and < 5 ULN

c) Suspected PBC

Exclusions:

1. No matter what liver disease, ALT > 5 X ULN

2. Active Hep B (HBs-Ag +) or C (anti HCV + & PCR- HCV-RNA +)

3. Any fibroscan score of > 3, active hepatitis, cirrhosis or evidence of portal hypertension.

Note: 1. Re hep B: It may be possible to treat these cases with anti-viral drugs and go ahead with transplant. 2. Re hep C. It may be possible to include these patients after they have

successfully completed course of anti-viral drugs. In ether case a hepatologist should be consulted for their opinion.

8. Psychiatric disorders

Note of Caution: Uncontrolled psychiatric disorder. Psychiatric disorders that are well-treated should not exclude patient. However, those who cannot attend follow-up due to their psychiatric illness should be excluded. This should be left to discretion of treating physician.

High doses of corticosteroids may be used during and after transplant. This could exacerbate certain psychiatric disorders.

9. Active drug or alcohol abuse

10. Infection

Uncontrolled acute or chronic infection, including HIV, HTLV-1/2 positivity.

11. Cyclophosphamide

If patient has received cyclophosphamide and they have no cytopenias they may be included.

However, if they have mild cytopenias with cell counts above those in section 5, they require a marrow aspiration to exclude myelodysplasia.

12. Compliance

Poor compliance of the patient as assessed by the referring physicians.

13. GAVE

Active or clinically significant gastric antral vascular ectasia (GAVE, "watermelon stomach"). Patients with GAVE must complete treatment for GAVE prior to entry into the treatment plan and may then be re-evaluated.

Note of Caution: Active or clinically significant GAVE means that there has been evidence of UGI bleeding or chronic iron deficiency with no other cause. The severity of the GAVE endoscopically is not related to the concept of “active or clinically significant”. Treatment of GAVE is difficult and usually not complete. Most endoscopists will not treat unless there has been bleeding. Thus treatment for GAVE need only be undertaken for those patients that the

endoscopist feels require treatment. As even after treatment there is still risk of bleeding during thrombocytopenia, the fitness of any patient with GAVE for AHSCT should be discussed between endoscopist, rheumatologist and transplant hematologist.

14. Smoking

Smokers: current, any amount - must have stopped for 3 months

15. Severe GI Disease

Severe GI disease defined as

a) The presence of malabsorption, b) The need for hyperalimentation, c) One or more episodes of pseudo-obstruction, and/or d) a ≥ 10% weight loss in association with the use of antibiotics for small intestinal bacterial overgrowth (SIBO) within the last year or esophageal stricture.

16. Uncontrolled hypertension

Further Notes of Caution:

These are issues that came up in discussion in the steering committee and with transplant haematologist but that were not included in the Delphi.

1. BMI. Our guidelines include weight loss from suspected GI disease. This recommendation was largely derived from previous exclusion criteria from trials. An issue discussed by the steering committee was whether weight loss from any cause should be considered similarly and whether absolute BMI should also be considered.

Absolute BMI: In Trials of Crohn's disease BMI ≤ 18 and serum albumin ≤20 g/L were exclusion criteria[1]. In as study of allogeneic transplants for malignant and non-malignant disease[2], the impact of BMI on non-relapse mortality (NRM) (as well as on "early" mortality, the majority of events for these endpoints being death without relapse) was most evident among underweight and very obese patients relative to those in the normal BMI group. Low BMI was <18.5, the same definition used by the CDC. Underweight subjects HR was 2.75, 95% CI (1.49-5.08). Only Thirty patients (1%) were underweight in this study. Results from the 2013-2014 National Health and Nutrition Examination Survey estimated that 1.4% of US adults age ≥20

years are underweight[3] so the proportion of underweight patients in this study was similar to the general population .

These results are also similar to a review of CIBMTR data in which Navarro et al[4] assessed the effect of BMI on transplantation outcomes in 4215 patients with AML undergoing a first HCT with either autologous stem cells (n = 373) or stem cells from related (n = 2041) or unrelated donors (n = 1801). The underweight group (BMI < 18.5) also had an increased risk of transplant related mortality (TRM) (RR, 2.23; *P* = .014).

In sum, this data suggests that a low BMI < 18.5 should be considered an important risk factor for poor outcome and should be weighed against potential benefit.

Weight Loss: The committee felt that a ≥ 10% weight loss in the last year, no matter what the etiology, might be an independent risk factor for poor outcomes. However, there was no consensus that this should be a definite exclusion criterion and the decision should be made by the rheumatologist and transplant hematologist.

2. Fertility issues should be discussed with patients in the reproductive period of life with consideration of semen cryopreservation in males and reproductive medicine consultation in females.

3. Skin Ulcers: Although not necessarily infected at the time of transplant, many skin ulcers may be at risk for infection during periods of neutropenia. On the other hand, some transplanters have seen improvement in ulcers after transplant. The risk of infection and its relationship to the number, size or location of ulcers is not known. The decision to exclude a patient based on skin ulcers should depend on a discussion between the rheumatologist and the transplanter.

In light of the fact that transplants will be performed before we have competed our Delphi exercise to develop these recommendations, the following recommendations have been adopted from the input of several cardiologists and the recent literature[5]:

1. WORKUP– All patients

1. Cardiac history (specifically symptoms of palpitations, dyspnea (New York Heart Association Class), presyncope and syncope.
2. Physical exam (specifically presence of right-sided heart failure: lower limb edema, ascites, murmurs, and elevated jugular venous pressure)
3. Bloodwork: high-sensitivity troponin, NT-proBNP
4. Resting ECG and 24-hour Holter monitor
5. Comprehensive transthoracic echocardiogram
6. Cardiac MRI with gadolinium. Consider adding T1 mapping sequences to suggested cardiac MRI protocol to evaluate for diffuse fibrotic processes that may be missed on LGE. It is understood that T1 mapping is not available at all centres but in the future our data may permit the development of cut-offs for T1 mapping times based on the outcomes of the patients in the cohort.

IF no exclusions on echo or MRI as below, then proceed to

7. right heart catheterisation measured before and after a 500 mL intravenous normal saline bolus,
    a. Fluid bolus not necessary if resting cardiac catheterisation pulmonary capillary wedge pressure (PCWP) was more than 15 mm Hg
8. Assessment of coronary artery disease
    a. CT coronary angiogram OR
    b. Coronary angiogram if risk factors for coronary artery disease
    c. Risk factors: Type II diabetes, age >50 years, male sex, strong family history of coronary artery disease, smoking history
9. Consider exercise testing

2. EXCLUSIONS

ON ECHO:

- LVEF <50%

- If global longitudinal strain (GLS) < -15% get MRI to determine EF
- Diastolic septal flattening (D-sign).
- Septal bounce if not secondary to benign conduction disease.
- Signs of significant pericardial disease (large pericardial effusion , signs of tamponade, constrictive pericarditis).
- severe RV enlargement (For example RV size > 50 mm or "apex forming") and severe RV systolic dysfunction (RV FAC < 25%, RV free wall strain <-15%)
- Grade III diastolic dysfunction as per ASE/EACVI recommendations for the evaluation of diastolic function

  see https://asecho.org/wp-content/uploads/2016/03/2016_LVDiastolicFunction.pdf
  - Note: any patient with Grade II diastolic dysfunction at significantly increased risk of fluid overload and congestive cardiac failure during transplant procedure so requires careful monitoring

ON ECG:

Arrhythmias that cannot be pharmacologically controlled, cardioverted or ablated.

ON HOLTER:

- Number of PVCs > 1000/24 hours – consider ICD insertion before transplant[6]
- Runs of non-sustained PVCs (3 consecutive PVCs with a rate >100 beats/min terminating spontaneously in less than 30 seconds)
- Sustained ventricular tachycardia

Record: frequent ventricular ectopic beats (VEBs) defined as occurring >30/h, non-sustained ventricular tachycardia (NS-VT) defined as >3 consecutive VEBs with a rate >100 beats/min terminating spontaneously in less than 30s, while sustained ventricular tachycardia (S-VT) defined as any VT whose ventricular rate ranged from 160 beats/min to 210 beats/min lasting 30s and/or requiring termination due to hemodynamic compromise less than 30s[6].

ON MRI:

- LVEF <50%.

- Diastolic septal flattening (D-sign).
- Septal bounce if not secondary to benign conduction disease.
- Constrictive pericarditis.
- Any LGE would be concerning for increased risk of transplant but at this point the exact extent that would preclude transplant is not known. any fibrosis present, this likely places the patient at much higher risk of SCD. The fibrosis creates the substrate for PVCs and eventually ventricular tachycardia that causes SCD. The presence of LGE should promote a discussion between cardiologist, rheumatologist and transplanter.

If echo and MRI provide discordant findings, follow the MRI.

ON RHC:

- end-expiratory PAPm > 25 mm Hg AND PVR > 3 Wood units
- mean end-expiratory PAWP > 15 mm Hg at baseline OR after 500 mL saline challenge.
- LVEF < 50%
- Non-revascularized severe coronary artery disease
- Cardiac tamponade
- Constrictive pericarditis

Other:

PAH on therapy

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