A Belgian consensus protocol for autologous haematopoietic stem cell transplantation in multiple sclerosis

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SUMMARY

Multiple sclerosis is considered to be an immune mediated inflammatory disorder of the central nervous system. It mainly affects young, socioeconomic active patients. Although our armamentarium for this disease has significantly evolved in recent years some patients remain refractory to conventional therapies. In these cases, autologous haematopoietic stem cell transplantation can be considered as a therapeutic option. Decreasing morbidity, mortality and increasing patient awareness have led to rising inquiry by our patients about this treatment option. With the aim of a standardised protocol and data registration, a Belgian working party on stem cell therapy in multiple sclerosis was established. In this paper, we report the consensus protocol of this working party on autologous haematopoietic stem cell transplantation in multiple sclerosis.
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INTRODUCTION

Multiple sclerosis (MS) is an immune mediated inflammatory disorder of the central nervous system, with a prevalence of 83 per 100 000 in Europe corresponding with an estimated prevalence of 88 per 100 000 in a 1991 survey in Flanders, Belgium.[1,2] Classically the disease has been divided into a relapsing remitting variant (RRMS) and progressive forms: secondary progressive (SPMS) if preceded by initial RRMS or primary progressive (PPMS) if progressive from disease onset. The immunopathology of relapsing forms is thought to be driven by a peripheral and adaptive autoimmune response whereas progressive forms are the consequence of a

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diffuse innate immune response within the CNS and neurodegenerative mechanisms triggered by uncontrolled chronic neuroinflammation.[3] This immunopathogical distinction is important since autologous haematopoietic stem cell transplantation (AHSCT) mainly targets the peripheral adaptive inflammatory arm of the disease and thus should only be considered in aggressive, treatment-refractory RRMS and progressive MS with substantial signs of ongoing inflammatory disease. Such an aggressive disease course has been estimated to occur in 4-14% of patients depending on the definition used.[4-6] Although a substantial increase in our therapeutic armamentarium has changed our treatment of MS in a drastic way optimal disease control remains elusive for many of these patients.[7] Originally supported by animal models and serendipitous clinical reports, AHSCT has been evolving since 1996 as a potential treatment for patients with severe autoimmune disease (ADs) refractory to conventional treatments. With this emerging clinical practice, the European Group for Blood and Marrow Transplantation (EBMT) Autoimmune Disease Working Party (ADWP) was created to perform multicenter retrospective studies and organise randomised controlled trials in MS and other ADs.[8,9] In 2012 Mancardi *et al.* reported the results of the Italian multicenter retrospective study including 74 patients treated with AHSCT with a BEAM/ATG conditioning regimen showing a sustained effect in suppressing disease progression (66% had stable or improved EDSS scores after five years). Patients in the relapsing-remitting phase of the disease were noted to benefit specifically.[10] In 2015 Burt and colleagues reported on 145 (123 relapsing-remitting MS, 28 secondary progressive) patients who underwent nonmyeloablative (cyclophosphamide and ATG in 129, alemtuzumab and cyclophosphamide in 22 patients) and unmanipulated haematopoietic stem cell transplantation.[11] This study showed similar results as the Mancardi cohort with significant improvement in disability (decrease in EDSS score of ≥1.0) in 41 patients (50%) at two years and in 23 patients (64%) at four years. Four-year relapse-free survival was 80% and progression-free survival was 87%. Moreover, the AHSCT-related mortality rate was 0% in this retrospective cohort. Currently, a randomised phase III study, called the MS International Stem Cell Transplant (MIST) trial, is underway to investigate AHSCT with a low-intensity conditioning regimen versus standard treatment in patients with RRMS. Results are expected to be available in the following year. Recently Nash and colleagues published their 5-year follow-up results of the Haematopoietic Cell Transplantation for Relapsing-Remitting Multiple Sclerosis (HALT-MS) trial, a prospective multicenter, single-arm, phase II clinical trial of high dose immunosuppressive therapy ("HDIT", in this case the BEAM protocol with CD34+ selection) and AHSCT for patients with RRMS. This study provided Class IV evidence that participants with RRMS experienced sustained remissions (91,3% of patients had stable or better EDSS scores with a mean follow up of 62 months) with toxicities as expected from HDIT/AHSCT and a treatment-related mortality rate of 0%.[12] The most stringent criteria of treatment effectiveness, termed 'No Evidence of Disease Activity' (NEDA: defined as absence of clinical and radiological disease activity (13)) are only attained in a fraction of conventionally (mainly interferons and copolymer) treated patients (7,9%) as witnessed by the cohort of Rotstein *et al.*[13,14] Compared to these 'conventional' treatment cohorts, AHSCT demonstrates much higher proportions of NEDA at two years (ranging in studies from 78% to 83%) and at five years (60%-68%).[15] These data seem even more impressive considering that MS patients who underwent AHSCT have much more aggressive disease if compared to clinical trial or cohort populations. Although safety has improved mortality rates for AHSCT in MS are still around 1-2% and thus should only be considered in patients with highly active inflammatory disease.[16,17] A recent meta-analysis summarises the evidence for AHSCT in MS as derived from pooled data on AHSCT in 764 transplant patients from fifteen studies (in any form of MS) over a 21-year period (1995 to 2016).[18] The meta-analysis demonstrated a transplant-related mortality of 2.1%, estimates being higher in trials conducted at earlier dates, for patients with a higher baseline EDSS, and for studies with a lower proportion of RRMS patients. The pooled rate of disease progression at 2 years was 17.1%, with 23.3% at five years. No evidence of disease activity was achieved in 83% and 67% of patients at two and five years respectively. A recent review by the same authors as the meta-analysis concluded that further trials are needed but stated that they "believe that enough evidence already exists to support the use of AHSCT for treatment of patients with aggressive RRMS and those with active RRMS in whom high-potency, approved, disease-modifying therapy has failed because of a lack of efficacy… We advocate healthcare organisations in all other countries to consider introducing AHSCT as the standard of care for these indications, and to regularly reassess and update their guidelines on the basis of new evidence that could alter the indications".[19]

METHODOLOGY OF CONSENSUS AGREEMENT

Within the Belgian patient population awareness of AHSCT as a therapeutic option for MS has grown, necessitating clear national guidelines for centres to support correct patient counselling. Moreover, uniform guidelines promote quali-

tative treatment and research perspectives. In this context, a working party on hematopoietic stem cell transplantation in multiple sclerosis was formed. Members were recruited based on the presence of combined centre expertise in AHSCT (clinical haematologists) and MS (neurologists). A questionnaire for neurologists and haematologists was conceived (See supplementary files one and two) based on the 2012 guidelines of the EBMT for AHSCT in severe autoimmune diseases.[20] All haematologists (9/9) and neurologists (9/9) filled out the questionnaire followed by separate haematologist and neurologist's meetings to reach consensus on the place and modalities of AHSCT in the treatment algorithm of MS.

AHSCT IN MS: COMMON DECISIONS FROM NEUROLOGISTS AND HAEMATOLOGISTS

Since correct patient counselling and data registration demand concerted evaluation and follow up by haematologists and neurologists the following decisions were made by the members of the working party:

Multidisciplinary evaluation by the neurologist and haematologist should take place at initial evaluation, day 100 after transplant and yearly thereafter. All the participating members agreed upon this. Time points of follow-up reporting are according to EBMT registration data (*https://www.ebmt.org/Contents/Data-Management/Registrystructure/MED-ABdatacollectionforms/Documents/13MS.pdf*). At these moments, neurologists and haematologists should exchange all necessary clinical data for optimal patient care and qualitative data registration as defined in paragraph *'Registry of AHSCT data from a neurological perspective'*. The way neurologists and haematologists discuss the patient consult can be defined based on the practicalities of the specific centres. More regular follow-up on an individual basis can be planned as needed according to good clinical practice.

Approval of the AHSCT protocol should be obtained from local ethics committees. Treatment protocols do not necessitate the approval of the ethics committee.[21]

As recommended in the EBMT 2012 guidelines **continual education within the applicable autoimmune domain** (e.g. multiple sclerosis) is advised.[20] All members agreed upon this as a mandatory element of good clinical practice. During yearly reunion research perspectives, protocol updates and AHSCT requests will also be reviewed.

Since the EBMT proposes AHSCT in autoimmune diseases as "clinical opinion (CO)" **written informed consent should be obtained from all patients**. Informed consent for AHSCT is already standard of care in all JACIE accredited stem cell transplant centres (*http://www.jacie.org/standards/6th-edition-2015*).

Biobanking is EBMT recommendation and possible in all nine centres.[20] Funding should be sought for systematic prospective biobanking.

The need for an external reviewing committee reviewing the file 'on paper' after the initial multidisciplinary evaluation in the treating centre was discussed. Since inclusion criteria are amenable for discussion, an external reviewing committee could be installed to provide uniform advice for patients and referring neurologists. After discussion, it was concluded that all 'clear cut cases' meeting all neurological and haematological eligibility criteria as stated in the consensus protocol should not need compulsory external reviewing. When in doubt or when deviation of standard criteria is deemed to be justified this should be discussed with the other members of the working party. Therefore, the patient file should be submitted to two neurologists and two haematologists, members of the working party (external to the requesting centre) and the four questioned physicians should agree on the indication for AHSC. During the yearly joint reunion, the protocol will be adjusted to current state of the art knowledge.

Since criteria, effectiveness and risks of AHSCT are still a matter of debate, inclusion of patients in a phase III study should be considered if available.

AHSCT IN MS: REGISTRY AND INDICATIONS FROM A NEUROLOGICAL PERSPECTIVE

REGISTRY OF AHSCT DATA FROM A NEUROLOGICAL PERSPECTIVE

Patient data on disease characteristics before and after AHSCT will be documented in a registry. Thus, timelines and all examinations were designed to be according to standard of care and good clinical practice as defined by the working party, stated below. Data will be registered in the local database of the involved centre (iMED, Edmus, etc.) and submissions of data in national (BELTRIMS) and international (MSBase) registries are encouraged.[22] Retrospective registration of disease course should be as detailed as possible for (at least) two years preceding the procedure. In order to optimise registration of the preceding disease course registration of patient data should be optimised in all Belgian (referral) centres. Follow-up as defined should be within the reference centre, if a patient wants to change his follow-up centre he should strongly be recommended to choose one of the other centres as defined in the working party. A reference centre is defined as a centre with a JACIE- accredited transplant unit and a neurologist with expertise in MS that have the necessary facilities to be compliant with the consensus protocol. For most centres of the working party the combined

expertise is within the same hospital-facility, for the MS & revalidation centre Overpelt transplants will be performed at the Jessa-hospital Hasselt. Of course, other centres can join the working party to apply as a reference centre.

After discussion, imaging follow-up with Magnetic Resonance Imaging (MRI) of the Brain and Spinal Cord was defined as follows:

- Time points: one month preceding the procedure, afterwards on month 6, 12, 18, 24, and thereafter on a yearly basis.
- Minimal brain MRI sequences were defined as: 3D Flair with thin slices, T1+-Gad, and 3D T1 consistent with MAGNIMS recommendations for follow up scanning.[23] The sequences encompass required elements for later volumetric assays. Since concerns were voiced about the potential accumulation of gadolinium with repeated imaging, evolving knowledge on this potential long term risk will be monitored and consequent adjustments to the protocol will be made according to new data.[24]
- MRI of (at least the cervical) spinal cord will be performed the month preceding the procedure, after one year and thereafter with 2-yearly intervals. Sequences should include STIR or PD, T2 and T1 (with and without Gd) consistent with MAGNIMS recommendations.[23]
- MRI follow-up should be performed on the same MRI-machine as much as possible to avoid inter-scanner variation.[25]

The clinical follow-up was defined as next:

- Follow up of Expanded Disability Status Scale (EDSS) with full evaluation of the Functional Systems (FS) scores on the month preceding the procedure and at month 3, 6 and thereafter at 6-monthly intervals.
- Registration of 9-hole peg test, timed 25 Foot-walk and symbol-digit modality test will be collected at the month preceding and thereafter yearly intervals. If time permits, the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) is advised for cognitive follow-up.
- Relapse history will be documented with description of symptomatology, anatomical location, need for steroid treatment (oral, intravenous, dosage, duration), duration of relapse, impact on EDSS with FS components should be documented during the relapse episode as well as the degree of recovery afterwards.
- Registration of side effects and complications. The potential relation to AHSCT should be documented.
- Treatment: Registration of all medications including Disease Modifying Treatments (DMT's) and symptomatic therapies.

CRITERIA FOR AHSCT IN RRMS PATIENTS

The following inclusion criteria were defined:

1. Age between 18-60 years.
2. MS diagnosis confirmed by McDonald criteria (2010).[26]
3. Maximum EDSS of 6, 5 (Exception for higher EDSS in cases of "fulminant" MS or important EDSS increase induced by a relapse in the last year with potential for recovery).
4. Disease duration ≤15 years from MS diagnosis.
5. Treatment failure after at least one highly effective treatment (two courses of alemtuzumab or at least six months of treatment with mitoxantrone, cyclophosphamide, natalizumab, rituximab, ocrelizumab).
6. Treatment failure is defined as the presence of the following criteria after at least six months of 'highly effective therapy (see point 5)':

- A documented clinical relapse.

AND

- MRI activity (brain or spinal cord imaging) defined as compared to a baseline scan (the time point of the baseline scan is not strictly defined as it can depend on the specific DMT) after initiation of highly effective treatment:
  - ≥1 Gad+ lesion

and/or:

  - ≥2 new T2 lesions

The following exclusion criteria were defined:

1. Patients not reliable to understand the risks and benefits of the procedure or unable to give written informed consent.
2. Previous treatment with AHSCT.
3. Contra-indication or inability to undergo MRI scans.
4. Recent suicide attempt or serious uncontrolled depression.
5. Haematological exclusion criteria as described in paragraph 6.5(?).

CRITERIA FOR PROGRESSIVE PATIENTS WITH ACTIVE DISEASE

Although initially separate criteria were proposed for patients with primary and secondary progressive disease, the working party decided that the 2013 revisions defining the clinical course of multiple sclerosis should be used.[27] In these criteria, progressive disease (whether from onset (Primary progressive) or after an initial relapsing course (Secondary progressive)) is divided in four groups depending on disease (in)activity (clinical relapses, gadolinium-enhancing activity, or new or unequivocally enlarging T2 lesions during the assessment period) and presence or absence of disease progression (defined as clinical evidence of disease progression, independent of relapses, over a given period of time in patients who have a progressive disease course). The working party members agreed that AHSCT should only be considered in progressive patients (whether primary or secondary) with important inflammatory disease activity. In this mindset, the following criteria for active progressive disease (with or without progression) were defined.

The following inclusion criteria were defined:

1. Age between 18-60 years.
2. MS diagnosis confirmed by McDonald criteria (2010). For primary progressive patient's presence of OCB is deemed necessary.
3. Maximum EDSS of 6, 5 (Exception for higher EDSS in cases of 'fulminant' MS or important EDSS increase induced by a relapse in the last year with potential for recovery).
4. Documented ongoing Progression since <5 years. Total disease duration of less than fifteen years.
6. Disease activity defined by the following criteria in the last twelve months:

- A documented clinical relapse.

AND

- MRI activity (brain or spinal cord imaging) in the last twelve months defined as compared to a previous scan in the last two years:
  - ≥1 Gd+ lesion

and/or:

  - ≥2 new T2 lesions

7. Since ocrelizumab is available in compassionate use for primary progressive patients these patients should only be considered in case of ocrelizumab treatment failure. Defined as the presence of the following after at least six months of treatment:

- A documented clinical relapse.

AND

- MRI activity (brain or spinal cord imaging) in the last twelve months defined as compared to a baseline scan (for the specific case of ocrelizumab the baseline scan should take place at least after eight weeks of treatment (based on ocrelizumab's documented activity MRI activity at week 8 (28))28:
  - ≥1 Gd+ lesion

and/or:

  - ≥2 new T2 lesions

For exclusion criteria see paragraph *'Recommendations for PBSC Mobilisation'*.

AHSCT IN MS: CRITERIA, PROCEDURE AND REGISTRATION FROM A HAEMATOLOGICAL PERSPECTIVE

REGISTRY OF AHSCT DATA FROM A HAEMATOLOGICAL PERSPECTIVE

All participating haematologists agreed with mandatory EBMT registration (MED-AB Data Collection Forms) at designated time points (day 0, 100 and yearly thereafter). As stated previously these time points correspond with multidisciplinary (neurologist-haematologist) patient follow-up and case discussion. Cases of failure from mobilisation should be reported to the EBMT or other registry. There is a need for lifelong follow up for secondary malignancies.

RECOMMENDATIONS FOR PBSC MOBILISATION

- Before mobilisation and HSCT, consideration should be given to chemotherapy-induced infertility (semen, oocyte or embryo cryopreservation as appropriate), risk of induction of premature menopause, and ultimate need for hormone replacement therapy, where appropriate. Pregnancy should be excluded within seven days of administering mobilisation or conditioning chemotherapy.
- Autologous stem cells may be derived from PB or BM. Mobilised PBSCs are preferred based on ease of procurement and better engraftment characteristics.
- Mobilisation procedures and stem cell processing should be performed in JACIE accredited collection centres.
- Priming chemotherapy is recommended to enhance mobilisation while maintaining disease control and to prevent potential flare, which may be a consequence of G-CSF alone.
- The recommended mobilisation regimen is CY at 2 g/m^2 with uromitexan (Mesna) protection and cautious hyper hydration followed by granulocyte-colony stimulating factor (G-CSF) 5-10 microgram/kg (level II).
- Before using CY for hematopoietic stem cell mobilisation in MS: electrocardiogram, and cardiac ultrasound evaluation in view of potentially fatal cardiac toxicity.
- A minimum dose of 3-5 x 10^6 CD34+ cells/kg should be collected.
- Back-up harvest is not recommended as a standard of care, especially since graft manipulation will not be undertaken.
- When CY-primed mobilisation fails, a second attempt at PBSC mobilisation or BM harvest should be considered following avoidance of immunosuppressive drugs, where possible. Despite the lack of evidence in patients with AD, the use of plerixafor (Not reimbursed in Belgium, only reimbursed for lymphoma and myeloma, if poor mobilisation to be negotiated with pharmaceutical company) and G-CSF may be reasonable in poor mobilisers after weighing up the benefits and risks. Steroid cover should be considered to reduce risk of disease flare related to G-CSF.

RECOMMENDATIONS FOR CONDITIONING REGIMEN

Cyclophosphamide (200 mg/kg in 4 days) + In vivo T-cell depletion with ATG (Thymoglobulin ®) 0.5 mg/kg of thymoglobulin (administered intravenously) five days before stem cell infusion, 1.0 mg/kg 4 days before, and 1.5 mg/kg on 3 days, 2 days, and 1 day before stem cell infusion.[11] With slow ATG administration concomitant steroids, antihistami-

nics and antipyretics should be administrated as per local guidelines.
On day zero, CD34+ hematopoietic progenitor cells will be thawed and infused.
Filgrastim (5 μg/kg/d) will be administered from day +5 until recovery of blood counts.

RECOMMENDATIONS FOR GRAFT MANIPULATION

There is no evidence to support ex-vivo graft manipulation, although decisions can be made on an individual patient basis. CD34 selection is not reimbursed in Belgium, increases the risk of infection, increases the recovery time of peripheral blood cell counts and requires harvesting a higher number of cells and is thus not recommended.

RECOMMENDATIONS FOR EXCLUSION CRITERIA FOR HSCT

- Pre-HSCT evaluation of heart, lung, kidney and gastrointestinal function is critically important. Patients with advanced cardiac disease (left ventricular ejection fraction <40%, uncontrolled ventricular arrhythmias, pericardial effusions), renal insufficiency (<30 mL/min per m^2), respiratory disease (clinical/subclinical ventilator impairment due to respiratory muscle involvement in MS) or active gastrointestinal bleeding should be excluded.
- Any uncontrolled acute or chronic infection, including HIV, human T-lymphotropic virus type 1 and 2, hepatitis B surface antigen positivity and hepatitis C PCR positivity, should be considered as a contraindication.
- Pregnancy should always be excluded within seven days of administering mobilisation chemotherapy or HSCT with a blood-based beta-human chorionic gonadotrophin assay.

RECOMMENDATIONS FOR INFECTION PROPHYLAXIS AND TREATMENT

Prophylaxis

- Pre-transplant workup should include screening for CMV, HSV, VZV, EBV, HIV, human T-lymphotropic virus type 1 and 2, hepatitis viruses and toxoplasmosis in all patients, with other infection screening appropriate for geographical location.
- CMV Ab-positive patients receiving ATG or other serotherapy, or receiving manipulated autografts, are recommended to undergo CMV PCR or antigenaemia screening for the first 100 days post-transplant.
- EBV Ab-positive patients receiving ATG or other serotherapy, or receiving manipulated autografts, are recommended to undergo EBV PCR screening for the first 100 days post-transplant, with active surveillance for post-transplant lymphoproliferative disease according to local practice.
- All patients should be accommodated in rooms, with appropriate clean air facilities (for example, laminar flow or HEPA) according to JACIE accreditation standards during BM aplasia/ severe neutropenia. Since the graft is T cell depleted these standards are according to allogeneic transplantation.
- All patients should receive broad-spectrum antibacterial (for example, quinolones) and anti-fungal prophylaxis (for example, azoles) during aplasia period and herpes prophylaxis (acyclovir) during at least 100 days post-transplant.
- All patients should receive prophylaxis against Pneumocystis jiroveci (PCJ) (for example, oral co-trimoxazole (TMP/SMX) three times weekly as tolerated or, if not tolerated, alternatives, such as monthly nebulized pentamidine, dapsone or atovaquone) for at least 100 days post-transplant.
- All patients positive for anti-toxoplasma antibodies should receive oral co-trimoxazole (TMP/SMX) daily until day –1, then after reconstitution of blood counts three times weekly for at least 100 days post-transplant.
- Consideration should be made to risk of reactivation of tuberculosis, with prophylaxis through the period of immune suppression where appropriate (level II).
- In carefully selected cases after weighing up the benefits, risks and costs, and only when repeated serious infections intravenous immunoglobulins replacement therapy may be considered.

Pre-emptive therapy

May differ according to local centre guidelines. If CD4 counts are used the following apply:

- Monitoring of CD4 counts once monthly until recovery to > 400 per microliter.
- Prophylaxis for PCJ and VZV until CD4 counts > 400 per microliter.
- Monitoring for CMV and EBV until CD4 counts > 400 per microliter.
- CMV reactivation (diagnosed by PCR or Ag) should be treated with intravenous ganciclovir (standard), oral valganciclovir (medical need though Belgian Hematology Society) or intravenous foscarnet according to centre policy and protocols.

Therapy of fever and proven infections

- Treatment of fever and established infection should follow centre policy and protocols since they may result in neurological deterioration in patients with MS.
- When a patient presents a new, high and well-tolerated fever at the time of neutrophil recovery, engraftment syndrome should be considered along with infective causes.

KEY MESSAGES FOR CLINICAL PRACTICE

Aims and goals of the Belgian MS-AHSCT working party:

1. **Establish a clear protocol and guidelines for AHSCT in the setting of adult Belgian MS patients.**
2. **Support and promote research in the field of AHSCT and other experimental (stem)-cell strategies (mesenchymal/other) in MS.**
3. **Promote continued education in the field of AHSCT for MS from a haematological and neurological perspective.**
4. **Organise a Belgian registry for AHSCT in MS.**

RECOMMENDATIONS FOR BLOOD TRANSFUSION

- Platelet and erythrocyte transfusions should be administered according to centre policy and protocols. Blood products should be irradiated.

CONCLUSION

AHSCT is a therapeutic option for treatment refractory MS. A Belgian Working party has been formed to standardise the indication, procedural measures and follow up in patients treated with AHSCT as described in this paper. Data will be collected in a prospective way to evaluate the results of this treatment option in the rapidly evolving treatment algorithm for MS.

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