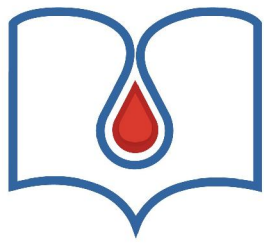


Hematopoietic Stem Cell Transfusion for Multiple Sclerosis Clínica Ruiz

Background:

Multiple sclerosis (MS) is a chronic inflammatory disease that causes destruction of central nervous system (CNS) myelin, with varying degrees of axonal damage. It mainly affects young adults (the symptoms appear around 30 years old), and is twice as common in women as in men. Studies published from the 1990s brought animal models and theoretical considerations of hematopoietic stem cell transfusion (HSCT) in the prevention and treatment of autoimmune diseases, (with clinical responses in some patients, suggesting that high-dose chemotherapy followed by HSCT rescue could “reset” the immunological changes through the control of autoreactive clones, followed by immunological tolerance after immune reconstitution. This led to the conclusion that HSCT may be a viable therapeutic option for MS. Autologous HSCT have been done in patients with MS since 1996 and more than 700 HSCTs have been performed around the world. Most patients were treated in small trials or in multicenter studies. In retrospective analyzes, a progression-free survival of more than five years after procedure has been observed, the neurological outcomes being considerably more favorable in patients with the relapsing-remitting type and/or those who showed an inflammatory pattern in magnetic resonance imaging (MRI) during the pre-transfusion screening. Reports of good results, particularly in the aggressive forms of MS reinforce the effectiveness HSCT in MS patients with prominent inflammatory activity. The risk of transfusion related mortality in HSCT for MS was conventionally considered important but has declined since 2001 to 1.3%, this probably being the result of the changes in the conditioning regimens, thus reducing toxicity. Recent data, with almost 500 autologous transfusions for MS in Europe, showed an

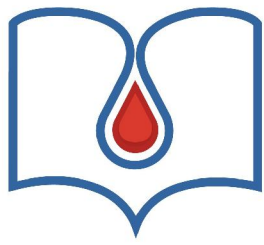


overall survival of 92% in five years and a progression-free survival of 46%, the main cause of mortality and morbidity being the recurrence of the autoimmune disease. The consensus on HSCT provides an indication of HSCT in patients with progressive MS unresponsive to conventional therapy and EDSS between 3.0 and 6.0. The forms of the disease that might benefit from the procedure are: relapsing remitting, primary or secondary progressive, and the “malignant” form, provided there is evidence of inflammatory activity at the time of transfusion indication.

Since 1993, scientists from the Centro de Hematología y Medicina Interna de Puebla (CHMI) have engaged in practicing HSCT using novel methods to both decrease the toxicity of the procedures and diminish costs. Over 500 HSCTs have been done in the CHMI for different diseases such as acute leukemia, chronic leukemia, aplastic anemia, myeloma, lymphomas, myelodysplasias and autoimmune diseases, including MS.

Method:

The “Mexican method” to autograft MS patients employs cyclophosphamide and rituximab as conditioning regimens. The method is started on an outpatient basis in all cases and completed on an outpatient basis in around 90% of individuals. Less than 10% of patients need to be admitted into the hospital.



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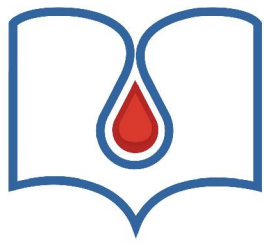
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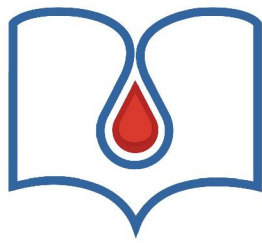
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Non-Myeloablative Hematopoietic Stem Cell Transfusion (HSCT)

For Autoimmune Diseases

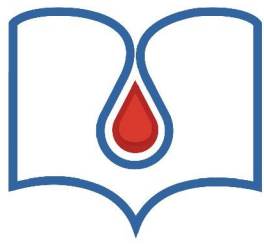
MEDICAL AND ACCOMODATION PACKAGE.

HEMATOLOGIA Y MEDICINA INTERNA SA DE CV.

Validity: December 31st 2017.

Inclusion criteria:

- Patients with MS having a relapsing-remitting course, even though other forms could also qualify: Secondary progressive (SPMS), primary progressive (PPMS) or progressive relapsing (PRMS).
- Patients must have a Karnofsky performance status above 70% and a EDSS score of 6 or below.
- Patients with an EDSS score between 6 and 7 will be accepted provided a capable carer accompanies them. Carer must be fully capable of transferring patient on and off the van, from and to the restroom, etc.)
- Patients with EDSS Score higher than 7 are not eligible for treatment at Clínica Ruiz.
- Patient must provide a recent central nervous system (CNS) MRI study (less than three months old).
- If a medical condition appears in the preliminary evaluations performed by our specialists that impedes the patient from receiving the transplant, the patient will be refunded. The only charges that will apply will be the ones consumed up to that point, such as, transportation, partial lodging and the evaluations performed.
- Patient has to be able to travel to and remain in Puebla, México or Monterrey, Mexico during a 28 day period, accompanied by a caregiver.
- We recommend to discontinue Immune Modulation or suppression medications 3 months before the transplant.
- Once patients show to comply with the inclusion criteria they will be officially added to the waiting list.
- As soon as openings are available patients will receive proposal dates.
- A video call through skype will be scheduled to answer any questions patients might have and further assess the eligibility for treatment prior to receiving an official date.
- Patients can only bring one carer at a time.
- Treatment must be fully paid two months prior to schedule treatment.



MEDICAL TREATMENT.

- Pre-testing to determine patient suitability for transfusion.
- CD34+ stem cell mobilization & collection (not including uncommon difficult mobilization cases requiring Plerixafor).
- Non-myeloablative conditioning (Cyclophosphamide + Rituximab).
- Unmanipulated hematopoietic stem cell graft infusion
- Engraftment recovery monitoring, blood testing and blood product infusions (if required).
- Final evaluation and check following engraftment recovery prior to patient departure.
- In the event patient develops complications (such as infection) that requires hospitalization & treatment, such services are available at full service hospital at additional charge.

Pre-transfusion Lab Testing

Several laboratory testing as well as spirometry, electrocardiogram and imaging.

Additional Pre-Transfusion Specialist Evaluations

- Cardiology evaluation
- Neurology evaluation

HSCT procedure & post-conditioning engraftment recovery

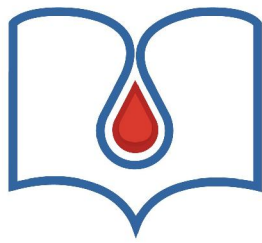
Autologous Transfusion Managed & Directed by Dr. Guillermo J. Ruiz Argüelles/ Dr. David Gómez Almaguer.

Regular follow ups by available hematologists: Dr. Guillermo J. Ruiz Argüelles or Dr. Guillermo J. Ruiz Delgado/ Dr. David Gómez Almaguer.

Medical staff consultation on-call 24/7 during the duration of the procedure.

Entire Uncomplicated HSCT Treatment Duration

26 Days Approximately



Routine Drugs Used for HSCT Procedure in the Appropriate Patient-Specific Adjusted Dosages

Medications Provided	UNITS
Rituximab (Only First Dose)	Variable
Cyclophosphamide	Variable
Filgrastim	Variable
Sulphametoxazol / Trimetoprim Anti-Infective Prophylaxis	28 tablets
Itraconazol Anti-Fungal Prophylaxis	15 capsules
MESNA	Variable
Pantoprazole	28 tablets
Dexamethasone	30 tablets
Ondansetron	60 tablets
Acyclovir	35 tablets

**Variable: Dosage is established based on body surface area or weight.*

Apheresis Stem Cell Collection

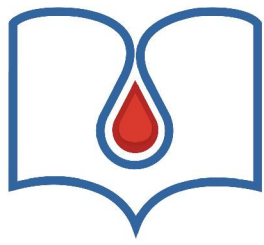
- Collection of Stem Cells:
 1. Mononuclear cell kit.
 2. Blood cell separator use.
- Cells preservation & storage from collection until reinfusion.
- Disposable materials.
- Medical staff 24/7 during the period of the transplantation.

Blood Product Infusions (if required)

Includes laboratory testing, application, disposable material and medical staff 24/7.
Compatible blood components available as needed. No need of a donor.

CATHETER.

Mahurkar catheter placement by a surgeon at Hospital if required or deemed necessary (Normal Procedure is Ambulatory, if overnight hospitalization is required costs must be covered by patient).



OUTPATIENT SERVICE.

The following services are included in the HSCT treatment cost:

- Patient MUST have accompanying carer (for assisting patient in preparing meals, personal care & assistance, etc).
- Transportation to/from airport.
- Transportation from and to apartment and the Clinic.
- Furnished apartment for accommodation of two people (patient + accompanying carer) with basic service (telephone, TV, internet access, washer/dryer).
- Daily apartment surface sanitizing during patient neutropenia.
- Pre-packaged processed food suitable for consumption during patient neutropenia (approximately 7-10 days).
- Available wheelchair
- Available on-site treatment facility English/Spanish translator.

*****Services not Required For Normal HSCT Treatment and Not Included in Treatment Pricing:**

Hospitalization if needed.

Additional Medications (Anything not listed above).

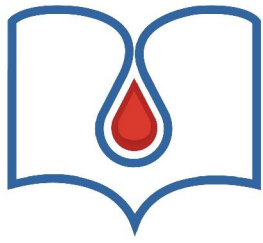
Additional Lab or imaging testing.

Additional Specialist Evaluations.

Five (5) Additional Bi-Monthly Rituximab Infusions (100mg) Recommended as Follow-up Treatment

Treatment must be paid two months in advance (via bank wire transfer)

For more information please contact dsmith@hsctmexico.com



Hematology and Internal Medicine

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