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WHAT IS HSCT?

Hematopoietic Stem Cell Transplantation (HSCT) is an established chemotherapy medical treatment demonstrated to be effective to halt disease progression in neurologic autoimmune diseases such as Multiple Sclerosis (MS), Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Transverse Myelitis (TM) and Neuromyelitis Optica (NMO), all of which are treated at Clínica Ruiz.

YOUR TREATMENT AT CLÍNICA RUIZ

You will receive world class medical attention with an innovative method that is internationally recognized. Through an outpatient based treatment program designed to provide maximum patient treatment safety, patients receive the best world class medical care at Clínica Ruiz. In addition, lodging and ground transportation are included to enhance convenience and comfort during your treatment stay.



Hematology
and Internal
Medicine

STATISTICS AND FACTS

We are the largest patient volume autoimmune disease HSCT treatment center in the world. Doctor Ruiz Argüelles and Doctor Gómez-Almaguer have performed more than 2500 HSCT procedures during more than 20 years for hematological and autoimmune diseases, out of which over 600 have been for MS. Our transplant related mortality is 0.16%, among the safest treatment records in the world. Positive results have been achieved in over 78% of patients transplanted at Clínica Ruiz, which includes both relapsing and progressive patients.

TREATMENT METHOD

The “Mexican method” to autograft MS patients employs high dose Cyclophosphamide and Rituximab as conditioning agents to eliminate autoreactive cells of the immune system responsible for damaging autoimmune disease. This treatment approach is a safe & tolerable, yet highly effective non-myeloablative chemotherapy regimen that has been shown to be highly effective to halt underlying autoimmune disease activity & progression. Serious treatment complications are rare, with fewer than 2% of patients requiring hospitalization.

TREATMENT TIMELINE

Extensive medical tests include review of patient MRI's (brain, cervical, thoracic and lumbar spine), chest X-ray, blood panel, electrocardiogram and spirometry. Consultation with neurologist, cardiologist and hematologist. Medical history.

To further mobilize stem cells from the bone marrow into the blood stream, subcutaneous filgrastim injections are given every 12 hours during a seven day period. These will be administered by clinic nurses and medical staff in the privacy of their apartment for their convenience and comfort.

Once sufficient stem cells have been harvested, two additional days of high dose chemotherapy are administered to further reduce white blood cells and suppress the majority of the existing immune system responsible for autoimmunity.

MEDICAL PRE-TESTING
DAY -13

1

CHEMOTHERAPY
DAY -11 & DAY -10

Two days of initial chemotherapy are administered to condition the immune system, eliminate autoreactive cells responsible for autoimmunity and to begin to mobilize stem cells into the blood stream.

STEM CELL MOBILIZATION
DAY -9 TO DAY -4

3

WEEK 1

STEM CELL HARVEST
DAY -3

Catheter placement, if necessary, takes place during an ambulatory outpatient procedure at the hospital. An apheresis stem cell collection procedure is conducted, whereby using an automated cell separator, stem cells required for the transplant are collected and stored at a controlled temperature.

CHEMOTHERAPY
DAY -2 & DAY -1

5

After the transplant, patients enter a period of minimum immune function called neutropenia. This varies from patient to patient, but usually appears between 48 and 72 hours after the transplant, and will last approximately seven to ten days. During this period, neutrophils, which are a type of white blood cell responsible for fighting infections are low. Diet and exposure are highly controlled, patients should follow the neutopenic recommendations provided.

Upon recovery a rituximab infusion is given in order to deplete any remaining lymphocytes. At this point patient can return home.

**NEUTROPENIC
PERIOD BEGINS
DAY +1**

**RITUXIMAB
INFUSION
APPROX DAY +11**

WEEK 2

6

STEM CELL
TRANSPLANT
DAY 0

Day Zero. Stem cells are given back to the patient.

7

8

**HEMATOLOGY
CONSULTATIONS UNTIL
RECOVERY
DAY +2, FWD**

Periodic hematology consultations every 48 hours. Blood samples and filgrastim injections will be performed until recovery.

WEEK 3

9

WEEK 4





WHY / HOW IT WORKS?

All immune cells in the body originate from a common progenitor, known as a hematopoietic stem cell (HSC) found in the bone marrow. As the HSC divides, it gives rise to a wide diversity of immune cell repertoire that all serve specific immune functions.

Many of these immune cells, known as lymphocytes, are capable of recognizing and defending against foreign pathogens that enter the body. For an, as yet, unknown reason, some of the lymphocyte immune cells develop a corrupted memory in which they become self intolerant and attack & damage the nervous tissue of the body. This is the fundamental mechanism that underlies autoimmune disease, and using chemotherapy to eliminate these self intolerant auto-toxic lymphocytes is the key to also halting the underlying autoimmune disease. **(Figure 1)**

The immune cells eliminated from the body are eventually replaced with new immune cells created in the bone marrow, and these new cells do not have the corrupted memory that causes the neurologic attack of autoimmune disease, thereby halting the underlying disease activity.

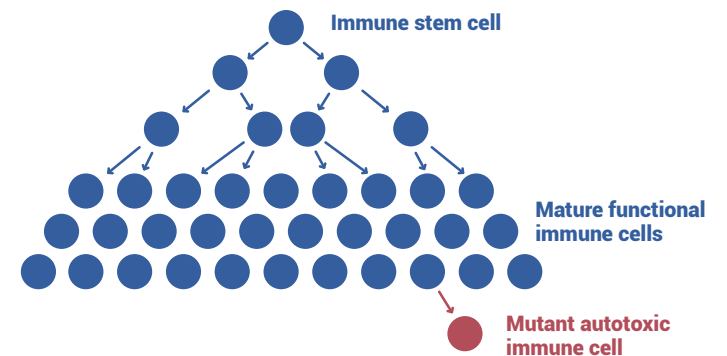


Figure 1

“ REGAIN CONTROL OF YOUR LIFE... STOP MS ”

In the same manner as normal cells divide, so does the mutant auto-toxic cell clone, giving rise to a large population of autoreactive cells that, in the case of neurologic autoimmune diseases, mediate damage of the myelin normal structure. This damage is the origin of all symptoms and signs associated to MS, NMO, CIDP and TM. **(Figure 2)**

What we will do to treat your condition in Clínica Ruiz, is remove auto-toxic immune cells from your system using both pharmacological as well as biotechnological drugs, followed by reinfusion of healthy precursor hematopoietic stem cells, known as the autograft, to begin producing new immune cells that will not attack the nervous tissue of the body.

In an early step of the treatment process, we will mobilize hematopoietic stem cells to your peripheral blood, and then harvest them by means of apheresis; a non-surgical procedure similar to dialysis where a

patient's blood is passed through a filtering machine by IV. Most patients can collect enough stem cells in a single sitting, but occasionally more than a single day may be required for the apheresis procedure.

These un-manipulated collected stem cells will be stored under very strict conditions in a standard blood bank refrigerator, where they remain healthy and viable until later being returned to the patient following chemotherapy. **(Figure 3)**

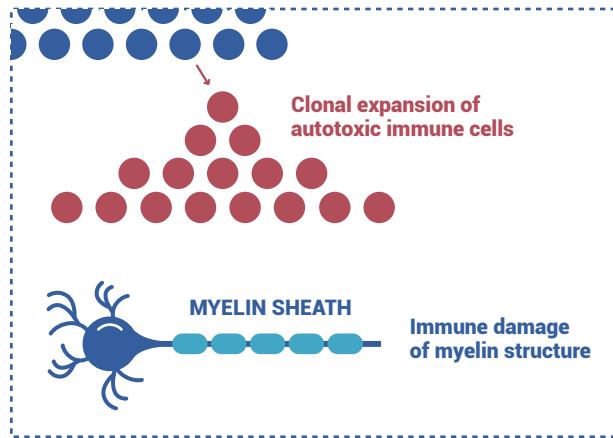


Figure 2

Store stem cells in
blood bank refrigerator

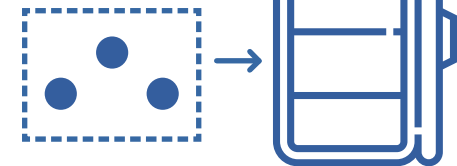


Figure 3

After your stem cells have been collected, chemotherapy is administered to further eliminate immune cells responsible for the underlying autoimmune disease.

Since drugs cannot selectively destroy auto-toxic immune cells, the only way to assure their removal is by wiping out all forms of dividing immune cells. This is why you will experience a temporary transient immunodeficiency during which you will have to undertake special precautions to avoid and prevent infection. This is temporary time period, which lasts 7-10 days, is known as neutropenia. **(Figure 4)**

When the cleaning of the immune cells is completed, your hematopoietic stem cell autograft will be retrieved from storage and infused back into your bloodstream. **(Figure 5)** Stem cells have the ability to naturally "home" into your bone marrow and start dividing again in a

healthy manner to repopulate your system with new immune cells. This is known as engraftment.

After a period of time your immune system will be restored with healthy cells, and devoid of auto-toxic cells. Additional immunotherapy specifically directed to mature B cells will be used in the event that a few autoantibody producing cells might have been stored and re-infused along with the stem cell autograft.

The aim of the entire HSCT treatment process is to stop the immune system from causing damage of the myelin so that proper electrical conduction within the nervous system is restored. In addition to the halting of the underlying autoimmune disease, the reinstatement of appropriate healthy signaling from nerves to muscles often results in clinical and symptomatic improvement.

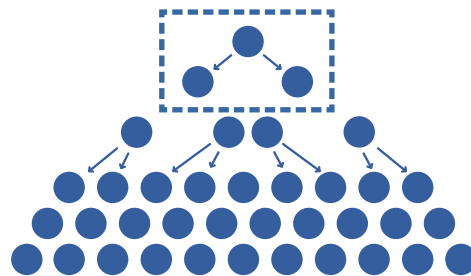


Figure 4

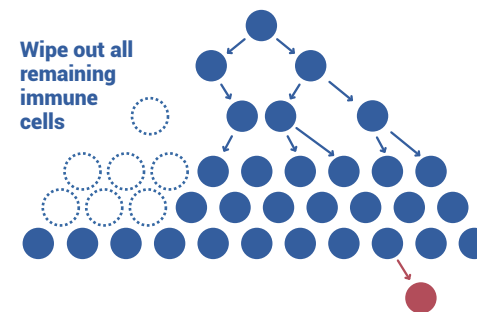


Figure 5



INCLUSION CRITERIA

<ul style="list-style-type: none"> • Patients with a confirmed positive diagnosis of the following neurologic disorders are eligible for HSCT treatment: <ul style="list-style-type: none"> - Multiple Sclerosis (MS): RRMS, SPMS and PPMS - Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) - Transverse Myelitis (TM) - Neuro Myelitis Optica (NMO / Devic's disease) 	✓
<ul style="list-style-type: none"> • Patients must be free of contraindicating health factors as determined by the clinic HSCT physician, and be deemed suitably healthy to safely tolerate the treatment. 	✓
<ul style="list-style-type: none"> • Patients should be able to self-transfer from one seated position to another, with the assistance of a caregiver. 	✓
<ul style="list-style-type: none"> • Patients with an Expanded Disability Status Scale (EDSS) up to 7.0 will be accepted for transplantation, pending all other acceptance factors. (If you do not know your EDSS please follow this link to self-evaluate) https://goo.gl/FAAGBh 	✓
<ul style="list-style-type: none"> • Patients in the range of EDSS 7.0-8.0 will be considered for transplantation based upon a pre-acceptance clinic doctor evaluation / assessment via Skype video. 	✓

<ul style="list-style-type: none"> • Patients may be considered for treatment based upon individual health status, without regard to age (no specific age restriction). 	✓
<ul style="list-style-type: none"> • Patient must provide a recent Central Nervous System (CNS) MRI study less than three months old from scheduled treatment date. All patients require an MRI, not just MS patients, to rule-out a pre-existing cancerous malignancy prior to undergoing HSCT. 	✓
<ul style="list-style-type: none"> • Patient has to be able to travel to and remain in Puebla, Mexico or Monterrey, Mexico during a 28-day period, accompanied by a caregiver. 	✓
<ul style="list-style-type: none"> • Immune Modulation or suppression medications must be discontinued at least three months prior to beginning the HSCT treatment process. 	✓
<ul style="list-style-type: none"> • 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. 	✓
<ul style="list-style-type: none"> • A video call through Skype will be scheduled to further assess the eligibility for treatment prior to receiving an official date. 	✓



MEDICAL RECORDS

- Two months prior to arrival patients must provide a Brain and full spinal (lumbar, thoracic and cervical) MRI Report that is no older than 3 months from scheduled treatment date. MRI may be with or without contrast, both will suffice. All patients require an MRI, not just MS patients, to rule-out a pre-existing cancerous malignancy prior to undergoing HSCT.
- Upon arrival patient must bring the CD with the scans themselves, it is not necessary to send them prior to treatment.
- It is mandatory that all immunosuppressive or modulation drugs be stopped 3 months prior to your scheduled treatment date. Please contact your general physician in order to suspend them accordingly.



WIRE TRANSFER

- Complete wiring instructions will be provided via email once patient has a confirmed date. Payment receipt must be sent as soon as it is issued. Payment must be fully paid two months in advance.
- Once the payment has reached our account our accounting department will send a receipt via email. Invoice will be issued on the month of treatment and sent to your email.



FLIGHT DETAILS

- Patient must be ready for traveling and staying in Puebla or Monterrey, along with a carer for a 28 day period.
- Travel itinerary must be provided to arrange collection at airport.

REQUIR



ADDITIONAL DOCUMENTS

• In order for us to invoice the service provided by the clinic we need you to send us the following documents:

1. Proof of Residence: This may be a document provided by your local tax authority, a driver's license or other document containing your address.
2. Passport scan



CAREGIVER

- Patient must be accompanied 24 hours 7 days a week during treatment. If necessary, care giving services are now available on behalf of Clínica Ruiz. If you are interested please ask for complete information and costs via email. (This service is subject to availability).
- Patients can only bring one carer at a time.
- Patients should not be around children under 12 years of age during treatment.



COST

The cost of the medical treatment and lodging during the procedure is \$57,500 US Dollars, which must be paid in full two months prior to confirmed date.

EMENTS

TREATMENT INCLUDES

PRE-TESTING TO DETERMINE PATIENT SUITABILITY FOR TRANSPLANTATION

- Chest X-ray, blood panel, electrocardiogram and spirometry.
- Consultation with neurologist, cardiologist and hematologist.
- Medical History

ROUTINE DRUGS USED DURING THE 26 DAY HSCT PROCEDURE IN THE APPROPRIATE PATIENT-SPECIFIC ADJUSTED DOSAGES

- Sulphamethoxazole / Trimethoprim
Anti-Infective Prophylaxis
- Itraconazole Anti-Fungal
Prophylaxis
- Cyclophosphamide
- Dexamethasone
- Pantoprazole
- Ondansetron
- Rituximab
- Filgrastim
- Acyclovir
- MESNA

APHERESIS STEM CELL COLLECTION

- Collection of Stem Cells (as many as required):
 - Mononuclear cell kit
 - Blood cell separator use
- Cells preservation & storage from collection until reinfusion.
- Disposable materials.

HSCT ENGRAFTMENT RECOVERY

- Engraftment recovery monitoring, blood testing and regular follow ups by available hematologists.
- Medical staff consultation on-call 24/7 during the duration of the procedure.
- Final evaluation and check following engraftment recovery prior to patient departure.

HSCT CONDITIONING

- CD34+ stem cell mobilization (not including uncommon difficult mobilization cases requiring Plerixafor).
- Non-myeloablative conditioning (Cyclophosphamide + Rituximab).

BLOOD PRODUCT INFUSIONS (IF REQUIRED)

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

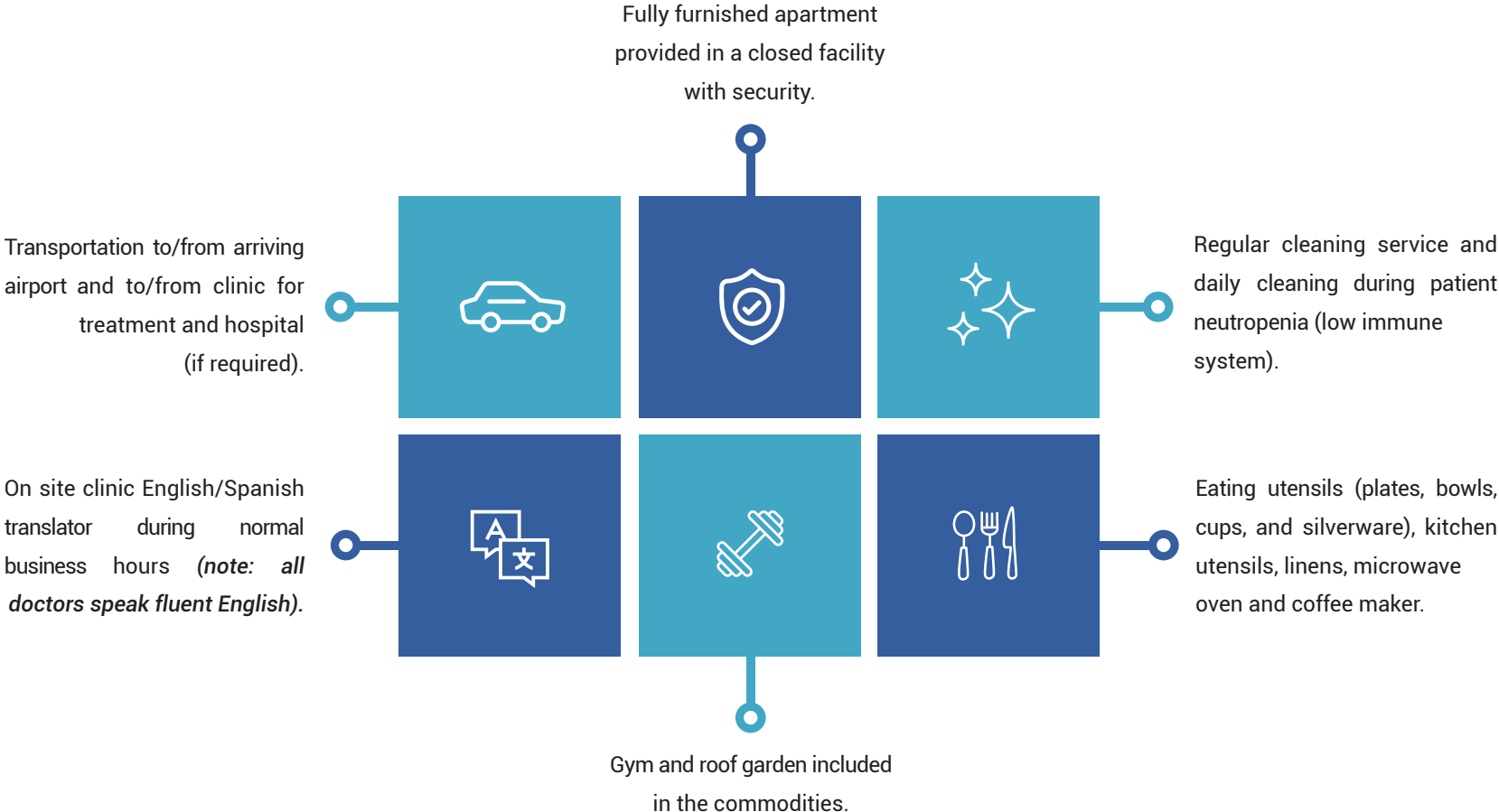
HSCT TRANSPLANT

- Unmanipulated hematopoietic stem cell graft infusion Managed & Directed by our medical staff.

PICC LINE INSERTION (IF REQUIRED)

- Mahurkar catheter placement by a surgeon at Hospital if required or deemed necessary.

ACCOMMODATION PACKAGE





Shower with hand rails, shower seat, available raised toilet seat adaptor with handles.



Alcohol hand sanitizer and bottled water.



Available Wheelchair, available walker.



Cable TV with 40 English channels, Broadband Internet service including WiFi, Landline telephone that includes free calling to most western countries (North America, Europe and Australia).

* FACILITY SELECTION

Dates will be offered based on availability in each facility. Patients must consider the following information in order to properly select their facility:

- Patients can only bring one caregiver at a time to the Puebla Facility. If a patient wishes to be accompanied by two caregivers at a time it is mandatory to travel to Monterrey. Apartments in Puebla are not adequate to fit 3 people, while Monterrey may easily accommodate up to 4. This only applies for overnight stays, meaning if you hire a 12 hour caregiver both facilities are eligible. There will be no exceptions to this rule.

- Puebla offers meal services at the cafeteria within the apartment building, each apartment is only equipped with a Refrigerator and Microwave. Monterrey has a complete kitchen in each apartment and no cafeteria service, grocery cards are provided in order to purchase monthly meals. If a patient has a special diet such as vegetarian, celiac, vegan or others it is strongly recommended for them to go to Monterrey in order to adhere to their dietary restrictions.

POST-TREATMENT RECOMMENDATIONS

Upon discharge you will be provided with specific instructions on how to return to normal life. As insight of these instructions we include the following:

HSCT FOLLOW-UP

Upon discharge post transplant patients will be contacted in order to assess their status and monitor their progress. Regular follow-up emails will be sent every three months from the following address: followup@hsctmexico.com during a 24 month period. We ask patients to check their email regularly and make sure it does not go to the spam folder. We appreciate your feedback.

TRAVELING

Unless it is for medical reasons it is recommended to avoid traveling for the first 6 months.

POST-TRANSFUSION

After treatment VACCINES are recommended, specific guidelines will be provided upon discharge.

PROPHYLACTIC MEDICATION MUST BE TAKEN FOR 6 MONTHS AS FOLLOW-UP INCLUDING:

Trimethoprim/sulfamethoxazole (TMP/SMX) 160/800 MG and Acyclovir 400 mg. Specific Dosages and prescriptions will be provided by our physicians, medication may be bought at the clinic or in your place of residence with the prescription we provide.

SURGERIES

Any type of surgery is not recommended unless it is strictly necessary. This is for a period of the first 6 months after the transplant.

NEUROLOGY FOLLOW-UP

We request patient's feedback regarding their EDSS score and overall health status post treatment. Our follow-up team will contact you via email and/or WhatsApp. We appreciate your compliance.

RETURN TO WORK

Due to the variable recovery period of each patient we encourage you to resume your normal life as much as you can tolerate. If you feel that you need a short term disability, we can approve it for up to three months.