

PIROGOV NATIONAL MEDICAL SURGICAL CENTER

A. A. MAXIMOV DEPARTMENT OF HEMATOLOGY AND CELLULAR THERAPY

**AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION (AHSCT)
FOR AUTOIMMUNE DISEASES (AID)**

GENERAL INFORMATION

What is Autologous Hematopoietic Stem Cell Transplantation (AHSCT)?

Autologous hematopoietic stem cell transplantation (ASHCT) is a type of transplantation that uses the person's own stem cells particularly from peripheral blood. These cells are collected in advance, stored at sub-zero temperatures, and returned at a later stage, after high dose chemotherapy or immunosuppressive therapy.

This is an established treatment for more than 3 decades and clinically approved for hematological malignancies (such as lymphoma, leukemia). Due to haemopoietic stem cell transplantation, the majority of the patients suffering from tumor blood diseases, who earlier were condemned to rapid death, obtained significant chances for recovery. As fundamental investigations have shown, the cause for development of autoimmune diseases is impairment of the cells of the immune system. It is not surprising that therapeutic methods, saving hematological patients, proved to be effective also in multiple sclerosis.

Thus, ASHCT is proposed as a new and promising therapy for autoimmune diseases (AID) patients, including multiple sclerosis (MS).

Lymphoablative Conditioning is a part of ASHCT. This procedure intends to **eradicate autoreactive immune cells in patient's body**, which destroy healthy tissues of the patients and may lead to development of AID. Chemotherapy dose for this procedure is less than in the established protocol for patients who have lymphoma or leukemia. The use of less intensive conditioning regimens is supported by the suggestion that AHSCT is not only immunosuppressive therapy, but also may have immunomodulation component. Moderate intensity and less toxic regimen may induce durable long-term remission, comparable with the high intensity regimens, but without being associated with the higher transplant-related mortality.

Experience of Pirogov National Surgical Center in ASHCT– effectiveness and toxicity (for MS).

The experience of Pirogov National Surgical Center in ASHCT for MS patients is the largest single center experience in the world. The analysis of quite large cohort of patients (more than 200 MS patients) with various types of disease course was performed. The core results of this study are presented below. It was shown that transplantation procedure was well tolerated by the patients, with no transplant-related deaths. Remarkably, no deaths were registered in this group

during the entire period of follow-up. The main early adverse events were febrile neutropenia (31,6%), mild and moderate hepatic toxicity (42,1%), transitory neurological deterioration (27,4%), diarrhea (7,4%), sepsis (3,2%), hemorrhage (3,2%), virus infections (2,1%), pneumonia (2,1%), fungal infection (1%), rash/allergy (8,4%). Long term side effects were fatigue (2-3 months after AHSCT) and alopecia (4-5 months after AHSCT). All side effects were predictable and controlled. Cumulative incidence of disease progression was 16.7% at 8 years after AHSCT. Estimated event-free survival at median follow-up of 48.9 months was 80%. These promising results might be due to the fact that our cohort of patients was relatively young (mean age – 35 years old) and not very disabled (median EDSS – 3.5). It is in line with the suggestion that the best candidates for transplantation seem to be relatively young patients with active inflammatory lesions of relatively short duration and rapidly progressive disease, but still low disability scores, resistant to conventional therapy. The advantage of our study is that we included patients with different types of MS. It was demonstrated that AHSCT may be effective in patients both with relapsing-remitting (RRMS) and progressive course (PrMS) of the disease. Cumulative incidence of disease progression was quite low both for RRMS and PrMS. It was higher in patients with progressive course of the disease than in those with relapsing-remitting MS: 21.3% vs 13.2%. For long-term follow-up (median 48.9 months), in the group with RRMS event-free survival rate was 83.3% and in the group with progressive course – 75.5%. Our results are comparative with the international experience. Notably, all patients without disease progression were off therapy throughout the post-transplant period. Another advantage of our study is that we included patients both with active CNS disease pre-transplant (40%) and those without. The latter ones did not have active lesions on MRI but they experienced clinical worsening and progression of disability. It was demonstrated that patients both with active CNS disease and those without may benefit from transplantation. It can be explained by the presence of occult inflammation not detectable with conventional MRI. In this situation, we consider that neurological progression even in the case of the absence of active lesions may be indication for AHSCT. In addition to clinical outcomes, we studied patient-reported outcomes, namely the quality of life (QoL) changes after AHSCT. QoL is an important outcome of MS treatment and its assessment provides the patient's perspective on the overall effect of treatment and allows for evaluation of patient benefits. Our results clearly demonstrate that AHSCT results in significant improvement of

patient's QoL. Improvement was shown at long-term follow-up both for the group with RRMS and for those with progressive course of the disease.

Eligibility Criteria for AHSCT

Inclusion Criteria

- Systemic autoimmune diseases
 - Diagnosed multiple sclerosis (all variants) with EDSS score between 1.5 and 6.5, documented progression/relapses over the previous year, with or without gadolinium-enhancing lesions.
 - Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) with or without paraprotein
 - Severe systemic vasculitis
 - Systemic lupus erythematosus
 - Systemic sclerosis
 - Crohn's disease
 - Other severe systemic autoimmune conditions, including connective tissue diseases
- Age 16 – 70
- Adequate organ function
 - Cardiac LV Ejection Fraction >45%
 - Total Lung capacity \geq 60%
 - Pulmonary artery pressure < 45 mmHg
 - DLCO/VA \geq 50%
- Absence of severe chronic infections
- Negative serology HBV, HCV, HIV
- Absence of mental and cognitive deficits and ability to provide informed consent
- Absence of gross cognitive disturbances
- Absence of severe concomitant diseases

Exclusion Criteria

- Any condition that affects normal functions of organs such as heart, kidneys, lung, liver etc. as this would limit your ability to receive high-dose chemotherapy immunosuppressive therapy with AHSCT
- Any active or long term infection caused by viruses, fungi or bacteria
- Uncontrolled diabetes
- A positive test for HIV, Hepatitis B and Hepatitis C
- Life expectancy is severely limited by another illness
- Evidence myelodysplasia or other non-autoimmune cytopenia
- Having received a cytotoxic agent within one month prior to AHSCT
- Pregnancy or at risk of pregnancy, including those unwilling to practice active contraception during the time of therapy
- Psychiatric illness, mental deficiency, or gross cognitive dysfunction
- Unability to give written informed consent in accordance with research ethics board guidelines
- High disability level in MS patients (EDSS>6.5) and/or stable non-active disease during the last 2 years.

Preparation before HSCT:

- You should treat all types of infections before AHSCT (urine tract infection, oral cavity, dental etc.)
- You should keep using all symptomatic medications (pain medicine, Fampyra, LDN, antidepressants) or medications for treatment comorbidities (high blood pressure, anticoagulants, diabetes treatment etc.). If you take steroids (prednisolone, dexamethasone, methylprednisolone) – keep using it.
- In spite of low risk of infertility (3-5% after lymphoablative protocol), we recommend to preserve sperm or embryo before AHSCT
- **You should stop using disease-modifying drugs:**

- a) **3 month before admission** - Natalizumab (Tysabri), Fingolimod (Gilenya), Dimethyl fumarate (Tecfidera), Interferon beta-1a (Avonex) (Rebif), Interferon beta-1b (Betaseron, Extavia), Glatiramer acetate (Copaxone), Laquinimod (Nerventra), Ibudilast (MN-166), Mycophenolata Mofetil (CellCept)
- b) **6 months before HSCT** - Teriflunomide (Aubagio), Lemtrada (Alemtuzumab), Novantrone (Mitoxantrone), Rituximab (Mabthera), Ocrelizumab (Ocrevus), Daclizumab (Zinbryta), Azathioprin (Imuran), Methotrexate, Cyclophosphamide (Cytosan), Cladribine (Leustat)

Pre-transplant examination:

- Full blood count
- Biochemistry screening
- Bacterial and virus screening
- Urine test
- Coagulation tests
- Chest X-ray
- Sinuses X-ray
- Spirogram
- ECG
- Ultrasound examination of abdomen, kidneys, pelvis (women)
- Heart ultrasound
- MRI examination – brain, cervix, thorax spine with Gadolinium - for MS and CIDP
- Examination by ophthalmologist (in case of necessary)
- Ultrasonic Doppler study

In case you need any additional tests (gastroscopy, computed tomography, Holter monitor etc.) will be prescribed.

Steps of AHSCT treatment

1. Stem cells stimulation - 4 days (sometimes 5-6 days, depending on the results of stem cell collection). Granulocyte-colony stimulating factor (G-CSF) 10 µg/kg.b.w./day (2 subcutaneous injections 11 pm and 3 am) in combination with steroid infusion (Methylprednisolone 500 mg) at 10am-11am (200 ml liquid for 20-40 min intravenous infusion). Also patient takes one antacid pill twice a day 30 mins before food (before breakfast and before dinner).

The most common side effects are: bone pain, headache, bad sleep, fever and other flu-like symptoms.

2. Insertion of special central venous catheter (dialysis) in external jugular or subclavian vein under ultrasound control for stem cell collection. Then chest X-ray control of catheter position.

3. Collection of stem cells (for 1 or 2, sometimes 3 days). To rebuild immune system, we need to collect 2 or more million hematopoietic stem cells per kg of body weight ($\geq 2 \times 10^6$ /kg/b.w. CD34+ HSC). Stem cells collection (harvesting) takes 5-6 hours (7-8 am – 1-2 pm). Autologous stem cell harvesting is performed by Haemonetics MCS+ multicomponent collections system or Spectra Optia Apheresis System.

4. Removing of dialysis catheter and insertion of new ordinary triple-lumen catheter in external jugular or subclavian vein under ultrasound control for chemotherapy and further treatment.

5. Chemotherapy (4 days) and stem cell reinfusion.

	Chemotherapy – pretransplant period					Transplantation
Day	-5	-4	-3	-2	-1	0
Cyclophosphamide mg/kg.b.w.	50	50	50	50	Rest (only supportive infusions 10 am – 3 pm)	Stem cell reinfusion Blood pressure and ECG monitoring, oxygen support, 3 L of normal saline with steroids and antihistamine
Total dose	200 mg/kg/b.w.					Urine testing after stem cell reinfusion

Chemotherapy (conditioning) takes 4 days. The main morning infusion of Cyclophosphamide with supportive medicine and hydration (3 L of normal saline) takes 3 h (usually 10 am – 1 pm). Second and third infusions (mesna uroprotection, nausea prophylaxis) – in 4 and 8 hours after the first one.

The most common side effects are: nausea, vomiting, diarrhea, constipation, oropharyngeal mucositis, alopecia, pancytopenia (low leucocytes, hemoglobin, platelets), hemorrhagic cystitis, fever.

From 1st day of chemotherapy we start antiviral, antibacterial and antifungal prophylaxis – Ciprofloxacin 1000 mg/d, Fluconazole 200 mg/d, Aciclovire 1200 mg/d, Co-trimoxazole (Bactrim) 960 mg/d on Mon, Wen, Fri.

Patient should take all tablets: pills for breakfast – patient takes one antacid pill before meals, other pills – after meals. Pills for lunch – patient takes one pill after meals. Pills for dinner - patient takes one antacid pill before meals, other pills – after meals. Patient has additional oral medications on Mon, Wen, Fri –Co-trimoxazole (2 white big pills –morning, evening).

We give 1 day for rest before stem cell reinfusion (D-1)

Stem cell reinfusion (D-0). After finishing chemotherapy, we provide stem cell reinfusion – D0 (transplantation day). We start stem cell infusion at 1-2 pm and finish at 3-4 pm. We recommend not to have meals after midday (12 pm), you can drink as much as you want. We remove the cryopreservation bags individually from liquid nitrogen and place them immediately in the water bath and thaw it. When thawed (-2-3 minutes), we infuse it as quickly as possible. Together with stem cells, we give fluids (3-4 L of saline), antihistamine, steroids and other symptomatic medications as needed. Also, we monitor heart rate (ECG), blood pressure, respirations, body temperature. Possible adverse reactions: nausea, coughing, vomiting, flushing, fever, dyspnea, chills, high or low blood pressure, allergy, low or rapid ventricular rate. Another side effects are pungent/tomato taste and smell, red-stained urine. We ask to urinate in special bag to assess a color of urine after stem cell reinfusion.

6. Isolation period (from D+1-D+3 to D+8-D+12).

Patient should never leave the room. Patient should keep the door closed. Medical staff will clean the room every day. Patient's suitcases will be removed. Patient should heat up food (approx. 10-20 seconds) in the microwave before consuming. Patient should use a special solution for mouthwash (mix half of cup of red solution with cap of water). Patient should use

provided chlorhexidine solutions for washing body – alcohol-containing for legs/arms/body, water-based - for genital area and head. Our staff will change bedding and wash clothing every day.

A patient must inform medical staff immediately of any problems or changes in condition.

Food Allowed during Isolation	Food Restrictions during Isolation
Tinned food – e.g vegetables or tuna, bread, coffee, tea, dried fruit, fruit juice, spices, herbs, lollies/sweets, nuts – roasted and salted	Fresh vegetables and fruits, milk and yoghurt products that don't conform to hospital standards
Processed food e.g muesli bars, packets of soup, noodles, pasteurized milk and yoghurt conforming to hospital standards	Raw nuts, toasted muesli – unless it is microwaved first, fresh fish e.g sushi, raw meat

We monitor blood pressure, heart rate, body temperature 3 times a day. Patient usually has supportive infusions – sodium saline, electrolytes, low-dose dexamethasone twice a day, G-CSF (subcutaneous shot, once a day at 3 pm) to decrease length of neutropenic phase. Additionally, we can use intravenous antibacterial, antiviral, antifungal medications when needed. We provide blood component transfusion when hemoglobin or platelet level is too low (Hb<80 g/L, Plt< 20 x 10⁹/L). Patient has 5th Rituximab infusion on D+10-D+12.

Discharge day is usually on D+12 - D+15.

General rules after discharge.

It can take a few months for your immune system to recover after autologous transplantation so it is important to take some sensible precautions to prevent infections during this time.

We recommend:

- To wear mask during first 3 months in public or crowded places (arriving/departure areas, supermarkets, metro etc.).
- To avoid contacts with sick people (like flu or chicken pox).
- In vast majority of cases we don't recommend vaccinations. After lymphoablative protocol patient has immune memory, additional vaccination can cause relapse of

autoimmune process.

- Monitoring of blood tests: total blood count, biochemistry screening - serum urea, electrolytes, creatinine, calcium, uric acid, blood sugar, liver function tests, C-reactive protein) in 2 weeks, then in 1 and 3 months after the discharge. Then if it's indicated.
- To monitor body temperature every evening during 1 month. In case of any signs of infection with/or without high temperature (>37.5C) or fever without signs of infection patient must go to hospital.
- GP (or hematologist) examination in 2 and 4 weeks after the discharge.
- Neurological observation in 3 months, then every 6 months with MRI results and EDSS re-scaling (for MS patients).
- MRI brain and spine in 3-6 months, then every 12 months (for MS patients).
- Specific examination (markers for AID, lumbar puncture for CIDP etc.) in 3 months, then according general rules for each condition.
- Posttransplant rehabilitation (under observation of neurologist and/or rehabilitation doctor/physiotherapist) – first 3 months at home. Public places like public swimming pools, gyms, health centers - in 3 month period.
- In most cases, we don't recommend antiviral, antibacterial and antifungal prophylaxis after lymphoablative protocol.
- We recommend it only for separate group with risk factors of infection: Levofloxacin 500 mg/day (1 tab) – 10 days, Fluconazole 100 mg/day (1 tab) – 10 days, Aciclovir 400 mg 3 times a day (or Valaciclovir 500 mg – twice a day) – 3 months; Co-trimoxazole 960 mg (2 tab – twice a day) - 3 times a week - Mon, Wen, Fri - 3 months.
- There is no risk to be in contact with family members if they are healthy
- There is no risk to be in contact with pets if they are healthy
- There are no special restrictions for sexual life if partner is healthy. We recommend to use contraception during 1 year after AHSCT.
- Food restrictions: fresh fruit and vegetables, milk products are available. We recommend to be careful with fast food, to avoid raw fish, meat (sushi, carpaccio

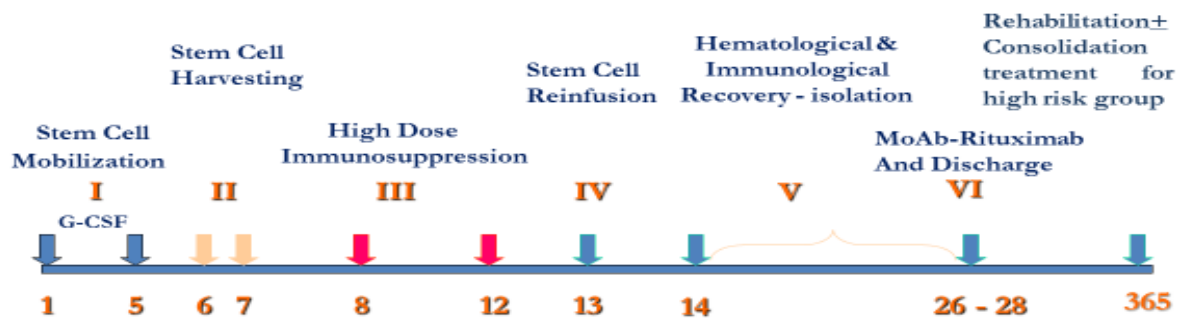
etc) within the next 3 months after discharge. All food supplements, vitamins which patient used before are available.

It's very important to follow 3 main rules: good mood (to be positive and keep strong belief in success), good food (follow healthy diet), active life style/rehabilitation (exercising).

Useful Information.

1. Stages of AHSCT (days):

AHSCT for AID (scheme)



2. Information for Admission to the Hospital:

- Patient should stop taking immunomodulating drugs in 3-6 months before admission (depending on variant of medication).
- When patients book flights, send them on email (msclerosis@yandex.ru). Our driver will meet you at the airport.

- About staying in hospital, it depends on personal recovery after immunoablative therapy (approximately 30 days). You can apply documents for tourist visa. We provide a room for patient for full period at treatment at the hospital.
- Patient doesn't need special preparing for treatment.
- It isn't required for a family member always to be present with the patient.
- Patient may be visited in the hospital and walk around outside. Patient will be isolated only during aseptic period (approx. 7-10 days).
- It's not very important to learn basic Russian

You should take with you clothes, slippers, laptop, medical records, personal hygiene. Our car will meet you in the airport arrival area with sign having your name. In our clinic, you will stay in single (isolation) ward. Your relatives will be able to visit you in the course of the day, until isolation period. The Wi-Fi Internet is available in the hospital. We recommend to use Tourist Hotel Complex "Izmailovo" (<http://www.izmailovo.ru/eng/>) for accompanying persons. After treatment, our doctor will give you all recommendations for recovery period. Recommendations are individual for each patient.

3. Contact Details:

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