Autologous hematopoietic stem cell transplantation in combination with immunoablative protocol in secondary progressive multiple sclerosis – A 10-year follow-up of the first transplanted patient

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Abstract

Introduction. Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system that affects young individuals and leads to severe disability. High dose immunoablation followed by autologous hematopoietic stem cell transplantation (AHSCF) has been considered in the last 15 years as a potential effective therapeutic approach for aggressive MS. The most recent long-time follow-up results suggest that AHSCF is not only effective for highly aggressive MS, but for relapsing-remitting MS as well, providing long-term remission, or maybe even cure. We presented a 10-year follow-up of the first MS patient being treated by immunoablation therapy and AHSCF. Case report. A 27-year-old male experienced the first symptoms - intermittent numbness and paresthesia of arms and legs of what was treated for two years by a psychiatrist under diagnosis of anxiety disorder. Zbog teške parapareze he was admitted to the Neurology Clinic and diagnosed with MS. Our patient developed aggressive MS with frequent relapses, rapid disability progression and transition to secondary progressive form 6 years after MS onset [the Expanded Disability Status Scale (EDSS) 7.0 Ambulation Index (AI) 7]. AHSCF was performed, cyclophosphamide was used for hematopoietic stem cell mobilization and the BEAM protocol was used as conditioning regimen. No major adverse events followed the AHSCF. Neurological impairment improved, EDSS 6.5, AI 6 and during a 10-year follow-up remained unchanged. Brain MRI follow-up showed the absence of gadolinium enhancing lesions and a mild progression of brain atrophy.

Conclusion. The patient with rapidly evolving, aggressive, noninflammatory MS initially improved and remained stable, without disability progression for 10 years, after AHSCF. This kind of treatment should be considered in aggressive MS, or in disease modifying treatment nonresponsive MS patients, since appropriately timed AHSCF treatment may not only prevent disability progression but reduce the achieved level of disability, as well.

Key words: multiple sclerosis, chronic progressive; hematopoietic stem cell transplantation; transplantation, autologous; treatment outcome; magnetic resonance imaging.

Apstrakt

Uvod. Multipla skleroza (MS) je imunski posredovana bolest centralnog nervnog sistema koja ugrožava mladu populaciju i dovodi do teških invaliditeta. Imunoablativna terapija u kombinaciji sa autolognom hematopoetskom transplantacijom matičnih celija (ATMĆ) poslednjih 15 godina smatra se potencijalno efikasnim terapeutickim pristupom za agresivnu MS. Najnoviji rezultati dugotrajnog praćenja pokazuju da ATMĆ nije efikasna samo za visokoagresivnu MS, već i za relapsno-remitentni oblik MS, obezbedujući dugotrajnu remisiju, možda čak i izlećenje. Prikazali smo rezultate 10-godišnjeg praćenja prvog transplantiranog bolesnika sa MS koji je lečen imunoablativnom terapijom i ATMĆ. Prikaz bolesnika. Bolesnik, star 27 godina, imao je prve simptome – povremenu ukočenost i parestezije ruku i nogu, zbog kojih je tokom dve godine lečen kod psihijatera pod dijagnozom anksioznog poremećaja. Zbog teške parapareze je primljen na Kliniku za neurologiju, gde je diagnostikovan MS. Njegov simptomi su se brzo napredovali i nakon šest godina od prve bolesti nastupio je prelazak u sekundarno progresivni oblik: proširena skala funkcionalne onesposobljivosti (EDSS) 7, Ambulatory Index (AI) 7. AHSCF je provedena, kiklofosfamid je korišćen za mobilizaciju hematopoetskih cell jele i BEAM protokol je koriscen kao preparacijski regimen. Nema većih zljedećih događaja koji bi nasledili AHSCF. Ujedno i njezin neurologLASki stanje se poboljšalo, EDSS 6,5, AI 6 i tokom 10-godišnjeg praćenja ostalo je neizmjenjeno. Braniću RMJ se pregledalo i otkrivena je nestanka gadolinije- enhancećih leća i manja progresije mozganog degeneracije.

Zaključak. Pacijent sa brzo osećanjem, agresivnom, neinflamatornom MS je načelno poboljšao i ostao stabilan, bez progresije invaliditeta tokom 10 godina nakon AHSCF. Ovaj vrhunski način lečenja treba da se prikaže u agresivnoj MS ili u pacijentima koji ne odgovaraju terapiji za proces nužne leće, jer vodljivo i vreme tretiranja AHSCF može ne samo preprećiti progresiju invaliditeta nego i smanjiti postignut razinu invaliditeta, kao i to.
noshi (EDSS) 7.0. Ambulation Index (AI) 7. Udara je
ATMC. Korišćen je cilioskofamid za mobilizaciju matičnih čelij za
skrivač, a BEAM protokol kao kondicioni režim, Nije bilo
značajnih neželjenih dejstava tokom i nakon ATMC. Došlo je
do poboljšanja neurološkog deficita. Skor EDSS bio je 6.5, AI
6 i tokom 10 godina praćenja ostao je nepromenjen.

**Zaključak.** Kod prizakog bolesnika sa agresivnom, neinflamatornom MS, nakon ATMC došlo je do poboljšanja neurološkog deficita i odsustva dalje progresije narednih 10 godina.

**Introduction**

Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system that affects young individuals and leads to severe disability. Available disease modifying treatment (DMT) such as interferon beta 1a, 1b and glatiramer acetate have proven to be effective in relapse reduction by around 30% in relapsing-remitting (RR) form of MS (RRMS) 1. However, relapse reduction is not achieved in at least 40–60% of RRMS patients and DMT does not diminish disability progression 2. Therefore, there is a subgroup of MS patients which deteriorate inspite of DMT, as well as those with aggressive MS which is characterized with a high relapse rate, rapid disability progression and a high magnetic resonance imaging (MRI) activity.

High dose immunoablation followed by autologous hematopoietic stem cell transplantation (AHSC) has been considered in the last 15 years as potentially effective therapeutic approach for severe cases of MS, RRMS and secondary progressive (SP) MS (SPMS) or those unresponsive to conventional therapies 2. The most recent long-term follow-up results suggest that AHSC is not only effective for highly aggressive MS but for RRMS as well, providing long-term remission, or maybe even cure 3,4. On behalf of European Bone Marrow Transplantation (EBMT) and European Charcot Foundation, Guidelines for autologous blood and marrow stem cell transplantation in multiple sclerosis were recomended in 2000 5. The concept of immunoablative therapy and AHSC is the induction of immune tolerance by resetting immune response in patients with MS, i.e. replacement of the dysfunctional immune system with the newly formed one 6,6.

We presented a 10-year follow-up of the first MS patient being treated by immunoablation therapy and AHSC in Serbia.

**Case report**

The presented patient, a military officer, experienced first symptoms – intermittent numbness and paresthesia of arms and legs, at the age of 27. He was treated by psychiatrist for 2 years as anxiety disorder. It was after developing severe paraparesis that he was admitted in our clinic and diagnosed with MS, according to the McDonnell criteria 7. In the next 3 years he had 6 relapses, affecting repeatedly brainstem and cerebellar functions. At that time he was under care of other neurologist and DMT was not recommended. He was seen again in our clinic, aged 34, when the course of MS was secondary progressive and the Expanded Disability Status Scale (EDSS) 6.0 8. At that point, DMT would not be justified and since he deteriorated rapidly – EDSS worsening by 1 point during 6 months, mitoxantrone (MTX) treatment was started. He received 12 mg/m² MTX, every 3 months, 3 times. During this treatment he further deteriorated for 0.5 point EDSS, reaching 6.5. At that point, AHSC was considered and thorough conversation was performed with the patient and his parents. He was informed about the procedure, potential risks and expected results. Ethical Committee of the Military Medical Academy, Belgrade, approved procedure and the patient signed informed consent in May 2005. Neurological examination revealed mild-moderate head tremor at rest, internuclear ophthalmoplegia, severe intention tremor of the arms, leg ataxia, as well as trunkal ataxia with inability to sit unless supported. Global muscle strength was preserved, deep tendon reflexes were symmetric and slightly hyperactive and plantar response was normal. His speech was slurred and he had difficulties while swallowing (he was able to drink on a straw and to eat only blended food). Gait was severely ataxic and he was able to walk with support of another person around 10 m. Vibration sense was lost at the level of the right rib frame and markedly decreased at the same level on the left side. Bowel, bladder and sexual functions were intact. Cognitive testing could not be performed considering limb ataxia and slurred speech. Overall, EDSS was 7.0, ambulation index (AI) 7 9, quality of life scale, Functional Assesment of Multiple Sclerosis being used 10, showed low scores on all the six domains tested – mobility, symptoms, emotional well-being, general content, thinking and fatigue, family and social well being. He was otherwise healthy. Physical exam was normal, as well as chest X-ray and abdominal ultrasound. Dental problems were sanated. ECG showed sinus rhythm, 72/min. All laboratory analysis needed for transplantation procedure were within normal range; magnetic resonance imaging (MRI) of the brain showed multifocal demyelinating lesions extensively within the supratentorial white matter, including juxtacortical and periventricular regions. The majority of the lesions were in the chronic stage with a diffuse giotic reaction. No gadolinium enhancing lesions were detectable. High grade atrophy, predominantly affecting the white matter was noted, with no significant regional predominance or asymmetry (Figure 1 A).

Peripheral blood stem cells were mobilized by using cyclophosphamide (4 g/m²) and human granulocyte colony-stimulating factor 10 mg/kg body weight. Intensive
rehidratation, alkalization and mesna (Uromitexan®) protection were used during cyclophosphamide infusion. A total nucleated cell and mononuclear cell (MNC) count was determined by flow cytometry (Technicon H–3) and 260 mL of cell suspension with 12.9 × 10⁸ MNC/kg was collected. For autologous stem cell cryopreservation, our own controlled-rate freezing protocol was carried out. No adverse events occurred during mobilization. The patient was discharged from the hospital in good health, with normal complete blood count (CBC) and biochemistry analysis, without signs of infection. The BEAM protocol was used as conditioning regimen – BCNU (carmustine) 30 mg/m², ARA-C (cytarabine) 800 mg/m², etoposide 800 mg/m², melphalan 140 mg/m², according to well-known and established oncological procedure. At the same time, in order to prevent side effects, the patient received antiviral, antibacterial and antifungal treatment. On day 0, AHSCT was performed and the patient received 260 mL cell suspension with 12.9 × 10⁸ MNC/kg.

Fig. 1 – a) Baseline magnetic resonance imaging (MRI) findings: axial T2 (TR 3241, TE 100), axial PD (TR 3241, TE 33), axial T2 (TR 3241, TE 100), axial T1 post-contrast (TR 610, TE 12). High-grade brain atrophy, infratentorial and periventricular white matter demyelinating lesions, no post-contrast enhancement are shown; b) MRI at the 2-year follow-up: axial T2 (TR 2100, TE 100), axial PD (TR 2100, TE 20), axial T2 (TR 2100, TE 100), axial T1 post-contrast (TR 613, TE 12). Mild progression of brain atrophy, a few new demyelinating lesions, no post-contrast enhancement; c) MRI at the 3-years follow-up: axial T2 (TR 2200, TE 95), axial PD (TR 2200, TE 35), axial T2 (TR 2200, TE 95), axial T1 post-contrast (TR 500, TE 14). Slight progression of brain atrophy, no new demyelinating lesions, no contrast enhancement; d) MRI at the 10-year follow-up: axial T2 (TR 5300, TE 72), axial PD (TR 2600, TE 86), axial T2 (TR 5300, TE 72), axial T1 post-contrast (TR 660, TE 20). Mild brain atrophy progression mainly infratentorial, no new demyelinating lesions, no post-contrast enhancement.
intra-venously without side effects and without hemolysis. During posttransplantation period, on days +1 and +2, the patient received rabbit antithymocyt globulin 7.5 mg/kg. The most pronounced myelosuppression was noted on day +7, white blood cells (WBC) 0.03 × 10^9/L (normal range 4.00–11.00 × 10^9/L), platelets was 10 × 10^9 (normal range 150–400 × 10^9/L), followed by petechial changes on skin and oral mucosa. The patient received six units of concentrated platelets and two units of concentrated erythrocyts. Since day +4 he was febrile (up to 38.2°C) and after isolation of coagulase-negative Staphylococcus form, the patient received antibiotics according to antibiogram. He was febrile during 6 days, without clinical and neurological deterioration. Repeated hemocultures remained sterile and the patient was discharged from the hospital, two weeks after transplantation, in good health. He had the same EDSS 7.0, CBS showing WBC 16.4 × 10^9/L with neutrophilia predominance, Hgb 102 g/L (normal range 110–180 g/L), red blood cells (RBC) 3.71 × 10^12 (normal range 4.4–5.8 × 10^12/L), platelets 98 × 10^9/L. Oral aciclovir was used as antiviral prophylaxis for six months post transplantation. Oral trimethoprim-sulfamethoxazole for Pneumocystis infection prophylaxis was continued for 6 months post-transplantation in alteration with ciprofloxacin. Antifungal prophylaxis with oral nystatin solution was continued for 6 months after the transplantation. He also continued with clonazepam for intention tremor. In subsequent monthly visits patient’s CBC completely recovered, while neurological improvement was noted 6 months post-transplantation. These include ability to swallow hard food, decrease in head tremor at rest, decreased intention tremor of arms, absence of truncal ataxia and comprehensible speech, which resulted in the EDSS decrease of 0.5, i.e. EDSS 6.5, AI 6. He was seen initially every 3 months, then every 6 months during the second and the third year and then yearly. No adverse events related to transplantation were noted. No relapses were recorded, his neurological status remained unchanged, EDSS 6.5, AI 6, marked improvement was noted on the quality of life scale, in subscales of general content, emotional well-being, additional concerns and social well-being. At a 10-year follow-up, EDSS was 6.5, AI 6. Brain MRI follow-up was performed after 2, 3 and 10 years (Figure 1, B–D).

**Discussion**

Our main expectations of immunoablation and AH SCT were related to disease stabilization – the absence of new relapses and sustained progression of disability. During a 10-year follow-up period the presented patient did not have relapses, nor disability progression. We even observed improvement in certain neurological functions 6 months after AH SCT which were sustained throughout the whole 10-year post transplantation period. These neurological improvements resulted in EDSS decrease of 0.5, better ambulation and marked improvement on the quality of life scale.

Our findings are in concordance with the recently published results on the long-term follow-up of AH SCT in MS 12–14. In the reported results progression-free survival (PFS) at 15 years was 44% in patients with active/inflammatory disease and 10% in those without inflammation, such as the presented patient. 13 After 5 years, EDSS improvement/stabilization was confirmed in 66% patients and after 7 years in 48% patients, including RR and SPMS patients. 14 The presented patient improved and decreased EDSS score for 0.5 six months post AH SCT which sustained for 10 years. Mancardi et al. 14 showed EDSS improvement of 0.5–1.0 within the first year after AH SCT, sustained for the subsequent years in 37% SPMS patients. Sustained EDSS improvement > 1 was confirmed in only 3% of SPMS patients and in 31% of RRMS. All the three published papers showed considerably better AH SCT outcome in RRMS, when inflammation is dominant pathological process and contributes to disability more than neurodegeneration. Neurological impairment caused by inflammation could be reversed by immunosuppression applied in AH SCT protocol, which explains improvement in EDSS score > 1 in one third of transplanted RRMS patients.

A pronounced effect on inflammation is confirmed by MRI results, showing a higher PFS and a better outcome in those with gadolinium+- lesions prior to AH SCT compared to those without MRI activity. 13, 14 The progression free survival (PFS) for these patients was found to be between 10% 13 and 46% at 5 years. 14 The presented patient did not have gadolinium+- lesions at baseline and remained progression free during a 10-year follow-up.

Noted improvements in our patient, as well as other SPMS patients reported, may be contributed not only to antiinflammatory effect of this protocol, since there was no MRI visible CNS inflammation, but to the known neurotrophic and neuroprotective effect of hematopoietic stem cell and resolution of conduction block 3, 6.

Transplantation related mortality (TRM) is one of the most important issues regarding AH SCT in MS. During 2001–2007, TRM in MS was reduced to 1.3%, from 7.3% in the previous period 1995–2000 14. Better patient selection and avoidance of high-intensity conditioning regimens resulted in a marked TRM reduction. There was no TRM in a recently published paper presenting Swedish experience of AH SCT in 52 patients with aggressive MS. 15 No mortality was reported in recent Russian 15 (95 patients) and Czech study 12 (26 patients) as well. Periprocedural toxicity such as fever, viral and bacterial infections or sepsis are not rare, nor insignificant, but they are well-managed in experienced hematological departments licensed for bone marow transplant. The only periprocedural complications in our patient were related to the period of the maximal myelosuppression, seven days posttransplantation. He had an episode of Staphylococcus coagulase negative bacteriemia, successfully treated with antibiotics and marked anemia and thrombocytopenia which needed transfusions. Analysis of all performed AH SCT has shown that older age (over 50 years), higher EDSS score (over 7.0), intense conditioning and/or extensive T-cell depletion protocol increase morbidity and mortality rate. 2

Concern was raised regarding brain atrophy after AH SCT, which was found to be 6% within the first posttransplant year, but afterwards return to 2% which is usual brain atrophy rate for MS patients. 16 Baseline brain MRI in the presented patient showed marked brain atrophy and a mild atrophy increase was noted 10 years after the transplantation.
Conclusion

The presented patient with rapidly evolving, aggressive, noninflammatory secondary progressive multiple sclerosis, initially improved and remained stable, without disability progression for 10 years, after the combined immunomodulative protocol and autologous hematopoietic stem cell transplantation. This treatment, performed as the palliative procedure led to progression-free survival for 10 years in the presented patient. Autologous hematopoietic stem cell transplantation should be considered in aggressive multiple sclerosis, or in disease modifying treatment nonresponsive multiple sclerosis patients, since appropriately timed autologous hematopoietic stem cell transplantation may not only prevent disability progression but reduce the achieved level of disability, as well.

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