



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

Autologna transplantacija matičnih ćelija u kombinaciji sa imunoablativnim protokolom kod sekundarne progresivne multiple skleroze – 10 godina praćenja prvog transplantiranog bolesnika

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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 (AH SCT) has been considered in the last 15 years as potentially effective therapeutic approach for aggressive MS. The most recent long-time follow-up results suggest that AH SCT 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 AH SCT. **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 psychiatrist as anxiety disorder. After he developed severe paraparesis 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]. AH SCT 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 AH SCT. 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 AH SCT. This kind of treatment should be considered in aggressive MS, or in disease modifying treatment nonresponsive MS patients, since appropriately timed AH SCT 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 matične ćelije (ATMĆ) poslednjih 15 godina smatra se potencijalno efikasnim terapijskim pristupom za agresivnu formu MS. Najnoviji rezultati dugotrajnog praćenja pokazuju da ATMĆ nije efikasna samo za visokoagresivnu MS, već i za relapsno-remitentni oblik MS, obezbeđujući dugotrajnu remisiju, možda

čak i izlječenje. Prikazali smo rezultate 10-godišnjeg praćenja prvog 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 psihijata pod dijagnozom anksiozni poremećaj. Zbog teške parapareze primljen je na Kliniku za neurologiju, gde je dijagnostikovana MS. Prikazani bolesnik oboleo je od agresivnog oblika MS sa čestim relapsima. Invaliditet je brzo napredovao i nakon šest godina od početka bolesti nastupio je prelazak u sekundarno progresivni oblik: proširena skala funkcionalne onesposoblje-

nosti (EDSS) 7.0, Ambulation Index (AI) 7. Urađena je ATMĆ. Korišćen je ciklofosamid za mobilizaciju matičnih ćelija iz krvi, a BEAM protokol kao kondicioni režim. Nije bilo značajnijih neželjenih dejstava tokom i nakon ATMĆ. Došlo je do poboljšanja neurološkog deficita. Skor EDSS bio je 6.5, AI 6 i tokom 10 godina praćenja ostao je nepromenjen. **Zaključak.** Kod prikazanog bolesnika sa agresivnom, neinflamatornom MS, nakon ATMĆ 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 progression¹. Therefore, there is a subgroup of MS patients which deteriorate in spite 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 hemopoietic stem cell transplantation (AH SCT) 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 therapies². The most recent long-time follow-up results suggest that AH SCT 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 recommended in 2000⁵. The concept of immunoablative therapy and AH SCT 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^{4,6}.

We presented a 10-year follow-up of the first MS patient being treated by immunoablation therapy and AH SCT 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 McDonald criteria⁷. 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

Ovu vrstu lečenja treba razmotriti kod agresivne MS, jer na vreme urađena ATMĆ može ne samo da spreči napredovanje invaliditeta, već i da redukuje neurološki deficit.

Key words:

multipla skleroza, hronična, progresivna; transplantacija hematopoeznih matičnih ćelija; transplantacija, autologna; lečenje, ishod; magnetna rezonanca, snimanje.

the course of MS was secondary progressive and the Expanded Disability Status Scale (EDSS) 6.0⁸. 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, AH SCT 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) 7⁹, quality of life scale, Functional Assessment of Multiple Sclerosis being used¹⁰, 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, f72/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 supra- and infratentorial white matter, including juxtacortical and periventricular regions. The majority of the lesions were in the chronic stage with a diffuse gliotic 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

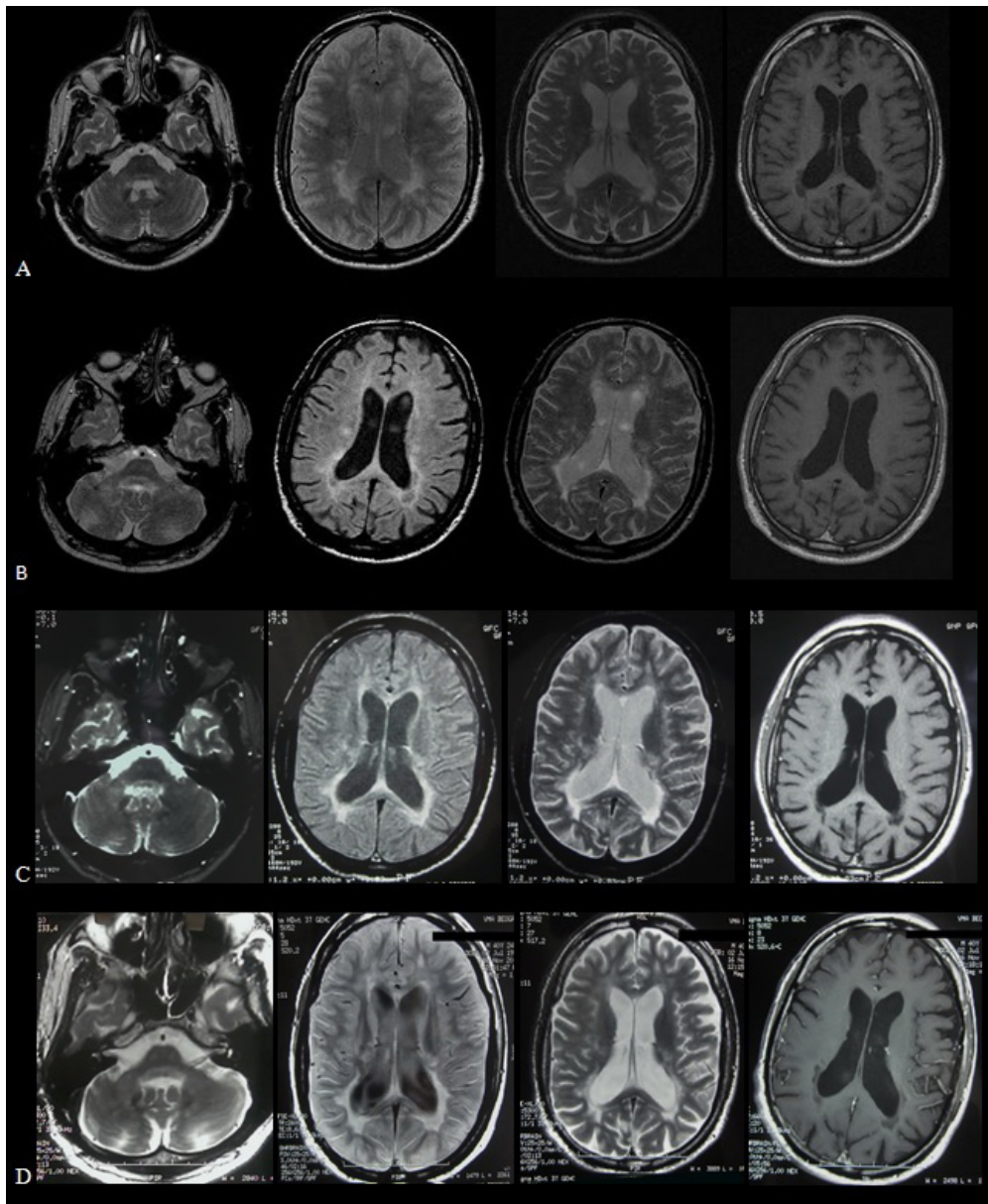


Fig. 1 – a) Baseline magnetic resonance imaging (MRI) findings: axial T2 (TR 3241, TE 100), axial PD (TR 3241, TE 33), axial T2 (TR 3241, TE 100), axial T1 post-contrast (TR 610, TE 12). High-grade brain atrophy, infratentorial and periventricular white matter demyelinating lesions, no post-contrast 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.

rehydration, 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 12.9×10^8 MNC/kg was collected. For autologous stem cell cryopreservation, our own controlled-rate freezing protocol was carried out¹¹. 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 12.9×10^8 MNC/kg

intravenously 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) $0.03 \times 10^9/L$ (normal range $4.00\text{--}11.00 \times 10^9/L$), platelets was 10×10^3 (normal range $150\text{--}400 \times 10^9/L$), 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 $16.4 \times 10^9/L$ with neutrophilia predominance, Hgb 102 g/L (normal range 110–180 g/L), red blood cells (RBC) 3.71×10^6 (normal range $4.4\text{--}5.8 \times 10^{12}/L$), platelets $98 \times 10^9/L$. 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 AHSCT 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 AHSCT 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 AHSCT 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

patient¹³. After 5 years, EDSS improvement/stabilization was confirmed in 66% patients and after 7 years in 48% patients, including RR and SPMS patients¹⁴. The presented patient improved and decreased EDSS score for 0.5 six months post AHSCT which sustained for 10 years. Mancardi et al.¹⁴ showed EDSS improvement of 0.5–1.0 within the first year after AHSCT, 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 AHSCT 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 AHSCT 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 AHSCT 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 years¹⁴. 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 AHSCT in MS. During 2001–2007, TRM in MS was reduced to 1.3%, from 7.3% in the previous period 1995–2000¹⁴. 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 AHSCT in 52 patients with aggressive MS³. No mortality was reported in recent Russian¹⁵ (95 patients) and Czech study¹² (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 marrow 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 AHSCT 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 rate².

Concern was raised regarding brain atrophy after AHSCT, which was found to be 6% within the first posttransplant year, but afterwards return to 2% which is usual brain atrophy rate for MS patients¹⁶. 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 immunoablative protocol and autologous hematopoietic stem cell transplantation. This treatment, performed as the palia-

tive 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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