Immunoablative therapy followed by autologous hematopoietic stem cell transplantation as the first-line disease-modifying therapy in patients with multiple sclerosis

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Introduction. Immunoablative therapy followed by autologous hematopoietic stem cell transplantation (AHSCT) is one of the possible disease-modifying therapies (DMTs) for patients with multiple sclerosis (MS). In this case series, we would like to present six patients with MS, who underwent AHSCT as the first-line DMT.

Case reports. Six MS patients with a rapid progression of disability with or without relapses underwent AHSCT as the first-line DMT at the University Hospital Ostrava between 2018 and 2021. The conditioning regimens for AHSCT used were a medium-intensity regime BEAM (Carmustine, Etoposid, Cytarabin, Melphalan) and low-intensity regime based on Cyclophosphamide. Four out of six patients showed some disability progression after AHSCT, so the rapid progression of MS was just slowed down by AHSCT. One patient developed activity on magnetic resonance imaging three months after AHSCT, and two experienced mild relapses during the follow-up period. None of our patients developed grade 4 non-hematological toxicity; all infections were mild. In one patient, an allergic reaction probably to dimethyl sulfoxide was observed.

Conclusion. Our case series of 6 patients shows that AHSCT is a promising therapeutic approach to slow down the rapid progression of clinical disability in MS patients with a good safety profile.

Key words: multiple sclerosis, immunoablative therapy, autologous hematopoietic stem cell transplantation

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INTRODUCTION

Multiple sclerosis (MS) is a chronic, inflammatory demyelinating, and neurodegenerative disease of the central nervous system[1,2]. Generally, MS treatment was conducted in the Czech Republic until 2022 with an escalation strategy of disease-modifying therapies (DMTs) (ref.[3]). In a proportion of MS patients with rapid progression of disability within a short period, starting high efficacy treatment (HET) would likely be a better option. However, the evidence is limited because pivotal trials were not focused on patients with aggressive MS (ref.[4]). Furthermore, only around 50% of MS patients can achieve no evidence of disease activity (NEDA-3) in 96 weeks on HET relating to all subjects across trials with HETs regardless of disease progression severity[5,6]. One possible therapeutic option may be immunoablative therapy followed by autologous hematopoietic stem cell transplantation (AHSCT). In a recent study, AHSCT as the first-line DMT showed overall cumulative NEDA-3 in 85% of patients during the median follow-up period of 30 months, and 95% improved on the Expanded Disability Status Scale (EDSS) (ref.[7]). This large metanalysis, including 15 studies (764 patients), showed the pooled rate of NEDA-3 at 83% two years after AHSCT and a good safety profile with a pooled transplantation-related mortality of 2.1%. In comparison with high-dose chemotherapy and AHSCT for multiple myeloma, transplant-related mortality is estimated as between 1 and 2% (ref.[8]). The conditioning regimens for AHSCT used in our patients were a medium-intensity regimen BEAM (Carmustine, Etoposid, Cytarabin, Melphalan) and slightly modified low-intensity regime based on Cyclophosphamide (Cy) according to Burt et al.[9]. In most cases, anti-T-lymphocyte polyclonal antibody (ATG) was added to increase the immunosuppressive potential[10]. Immunoablative therapy is followed by AHSCT to shorten the period of aplasia; long-lasting aplasia can lead to life-threatening infections. The collection of hematopoietic stem cells (HC) is always made by leukapheresis after the mobilization chemotherapy, which precedes immunoablative therapy. As a chemotherapeutic regimen for mobilization, we used Cy with subsequent administration of granulocyte colony-stimulating factor (G-CSF) injection in all cases.

In this case series, we would like to present our experiences and results of six patients with rapid progression of disability with or without relapses who underwent AHSCT as the first-line DMT at the University Hospital Ostrava between 2018 and 2021.

CASE REPORTS

Case 1

A 23-year-old woman without any comorbidities experienced relapse of severe vertigo accompanied by lower limb weakness and deterioration of fine motor skills in May 2016. Her first examination in our MS center was in January 2017; she reached EDSS 2.5. During this month, she experienced severe relapse with deterioration of EDSS to 5.5. She received 4 g of intravenous methylprednisolone (MPIV), followed by 6 series of therapeutic plasma exchanges (TPE) without any improvement. In the next visit in April 2017 her EDSS was 6.0, and later in July 7.0. She was again treated with MPIV (5 g) and 4 series of TPE after which we decided to perform AHSCT. She received immunoablative therapy consisting of the BEAM + ATG regimen, and in June 2018, the autologous transplant was reinfused. The complications of AHCST were not serious – only febrile neutropenia and mild clostridial enterocolitis were observed. She was stable until November 2020, when she experienced a mild relapse without any change in her EDSS. She was treated with 3 g of MPIV. The subsequent mild relapse appeared after two years in March 2022. The patient reached EDSS 7.5 and was treated with 5 g of MPIV. During the whole time, further MRI scans showed no MS activity.

Case 2

A 43-year-old man without any comorbidities started experiencing progressive difficulties in walking and left lower limb weakness in January 2018. He was diagnosed with MS in July 2018, when MRI and lumbar puncture (LP) were performed and he was treated with MPIV (3 g). In the first visit at the MS center in October 2018, his EDSS was 5.5. Since there was no available treatment in the Czech Republic at that time, considering the aggressive course of the disease, the patient was indicated for AHSCT. The immunoablative regimen consisted of Cy and ATG, and reinfusion of the autologous transplant was performed in March 2019. The complication of the AHSCT was mild febrile neutropenia. After AHSCT, the patient's EDSS improved to 4.0. He was stable until May 2020 when a mild relapse occurred. The EDSS at that time was 4.5, and he was treated with 5 g of MPIV. The last clinical follow-up was in April 2022, and the patient's last EDSS was 5.0. Further brain MRI scans showed no signs of progression.

Case 3

A 43-year-old man with chronic limb ischemia and polyneuropathy of the lower limbs was admitted to our inpatient department for progressive lower limb weakness and urinary retention in September 2018. An acute MRI scan of the lumbosacral spine showed myelitis of the distal thoracic spinal cord, and subsequent brain MRI and LP confirmed the diagnosis of MS. During hospitalization he was treated with 3 g MPIV. His first examination at the MS center was in February 2019, when his EDSS was 6.0, and AHSCT was recommended. The immunoablative regimen consisted of Cy and ATG, and reinfusion of the autologous transplant was performed in June 2019. There were three complications of AHSCT: 1) allergic reaction during transplant administration was probably due to the toxicity of dimethyl sulfoxide (DMSO), which is used as a cryoprotectant for cryopreservation of the HC, 2) a persistent fever of unknown origin a month after AHSCT, and though no etiology agent was found, the fever went away after moxifloxacin treatment, 3) cytomegalovirus (CMV) viremia, which was considered as a CMV reactivation and managed by antiviral therapy. The patient was stabilized on EDSS 6.0 until October 2020 when he progressed to EDSS 6.5. The next course of the disease was stable, without further progression or MRI activity.

Case 4

A 16-year-old girl without comorbidities was admitted to the district hospital with an intermittent impaired sensation in the right foot, left leg, right little finger, and weakness of the right upper limb lasting for five months in August 2019. Due to confirmed diagnosis of MS (brain and spinal cord MRI and LP confirmed diagnosis), she was transferred to our pediatric department, where she was treated with MPIV (4.5 g) and 3 series of TPE without any improvement. Her first EDSS was 7.0 and we decided to perform AHSCT. The transplantation was performed in December 2019 after immunoablative treatment which consisted of Cy + ATG. There was no complication of AHSCT. Her EDSS improved after mobilization to 4.5, and 2 years later, it was 4.0, which persisted until the end of the follow-up. We observed no relapses or MRI activity during the follow-up.

Case 5

A 29-year-old man without comorbidities was firstly examined in the district hospital due to a fall from a ladder and loss of consciousness with convulsions in April 2018. After the injury, tingling in all limbs persisted, and he limped on his left leg. Brain MRI and LP confirmed MS diagnosis in September 2018, and 3 g of MPIV were administrated. At the initial visit in December 2018 at the MS center, his EDSS was 3.5. Three months later, the patient's condition deteriorated, he could walk only 500 meters, and the EDSS worsened to 4.5. He was treated with MPIV (3 g) and 3 series of TPE, unfortunately without any effect on disability progression. On the next visit, in June 2019, his EDSS was 6.0, and AHSCT was recommended. The immunoablative regimen consisted of Cy and ATG, and reinfusion of the autologous transplant was performed in August 2019. The early post-transplantation period was complicated by mild febrile neutropenia (urinary infection). However, even though the AHSCT did not stop the progression, EDSS three months, and one year after AHSCT was 7.0 and 7.5, respectively. Follow-up

Table 1. Characteristics of our cases and their clinical and radiological development after AHSCT.

Case	1	2	3	4	5	6
Age at disease onset (years)	23	43	43	16	29	31
Sex	F	M	M	F	M	F
OCB (CSF/serum)	16/0	10/0	18/1	15/0	12/2	27/2
Presence of Gd+ lesion(s) on the first MRI	1	1	0	1	1	0
Interval between first symptoms and AHSCT (months)	25	12	11	8	16	52
AHSCT regime	BEAM + ATG	Cy + ATG	Cy + ATG	Cy + ATG	Cy + ATG	Cy + ATG
Follow-up after AHSCT (months)	45	38	33	28	31	4
Baseline EDSS	7.0	5.5	6.0	7.0	6.0	7.0
EDSS 3 months after AHSCT	7.0	4.0	6.0	4.5	7.0	6.5
EDSS 12 months after AHSCT	7.0	4.0	6.0	4.5	7.5	–
Last EDSS	7.5	4.5	6.5	4.0	7.5	6.5
Number of relapses after AHSCT	2	1	0	0	0	0
MRI activity after AHSCT	0	0	0	0	1	0

F: female; M: male; OCB: oligoclonal bands; CSF: cerebrospinal fluid; AHSCT: autologous hematopoietic stem cell transplantation; EDSS: expanded disability status scale; Gd+: gadolinium-enhancing; MRI: magnetic resonance imaging; ATG: thymoglobulin; Cy: cyclophosphamide; BEAM: Carmustine, Etoposide, Cytarabine, Melphalan.

Table 2. Complications of AHSCT.

Case	Engraftment in leukocytes after AHSCT	Engraftment in platelets after AHSCT	Non-hematological toxicity
1	D+8	D+10	Febrile neutropenia grade 3 Mucositis grade 2 Enterocolitis infectious grade 2
2	D+9	D+9	Febrile neutropenia grade 3
3	D+8	D+7	Cytomegalovirus reactivation grade 2 Allergic reaction grade 3 Fever grade 1
4	D+10	D+10	Vomiting grade 2
5	D+9	D+10	Febrile neutropenia grade 3
6	D+9	D+9	Febrile neutropenia grade 3 (Urinary infection) Alanine transaminase elevation grade 3 of unknown origin

AHSCT, autologous hematopoietic stem cell transplantation; Engraftment in leukocytes, neutrophil count > 1x10e9/L; Engraftment in platelets after, platelets count > 20x10e9/L.

brain MRI 3 months after AHSCT showed new and enlarging T2 lesions and active lesion according to diffusion-weighted imaging. The next MRI showed no activity.

Case 6

A 35-year-old woman experienced gait worsening for more than four years, rapidly deteriorating in June 2021. She could walk a maximum of 10 meters with a walker; she also had sphincter dysfunction, memory impairment, and pain in all limbs and eyes. Brain and spinal cord MRI and LP confirmed MS diagnosis. Her first visit at MS center was in October 2021, her EDSS was 7.0, and AHSCT was indicated. She was transplanted after immunoablative therapy (Cy + ATG) in November 2021. The early post-transplantation period was complicated by urinary infection (febrile neutropenia) and hepatopathy (alanine transaminase elevation grade 3 of unknown origin). In March 2022, her EDSS improved to 6.5.

DISCUSSION

Our case series shows that AHSCT is a promising therapeutic approach to slow down the rapid progression of clinical disability in MS patients. Four out of six patients showed some progression in EDSS. Hence, the rapid progression of MS was just slowed down by AHSCT. The EDSS improved after AHSCT in three patients; however, the cumulative median EDSS was the same as before (EDSS 6.5). Only one patient developed new and enlarging T2 lesions on MRI three months after AHSCT and continued disability progression and two patients experienced mild relapses during the follow-up period. Das et al. published even better results with no relapses in their study, which consisted of 20 patients. The median interval between diagnosis and AHSCT was five months, a shorter period than in our patients[7]. In our study, the median time from diagnosis to AHSCT was seven months, and between first symptoms of MS and AHSCT 14 months, which was influenced by two pa-

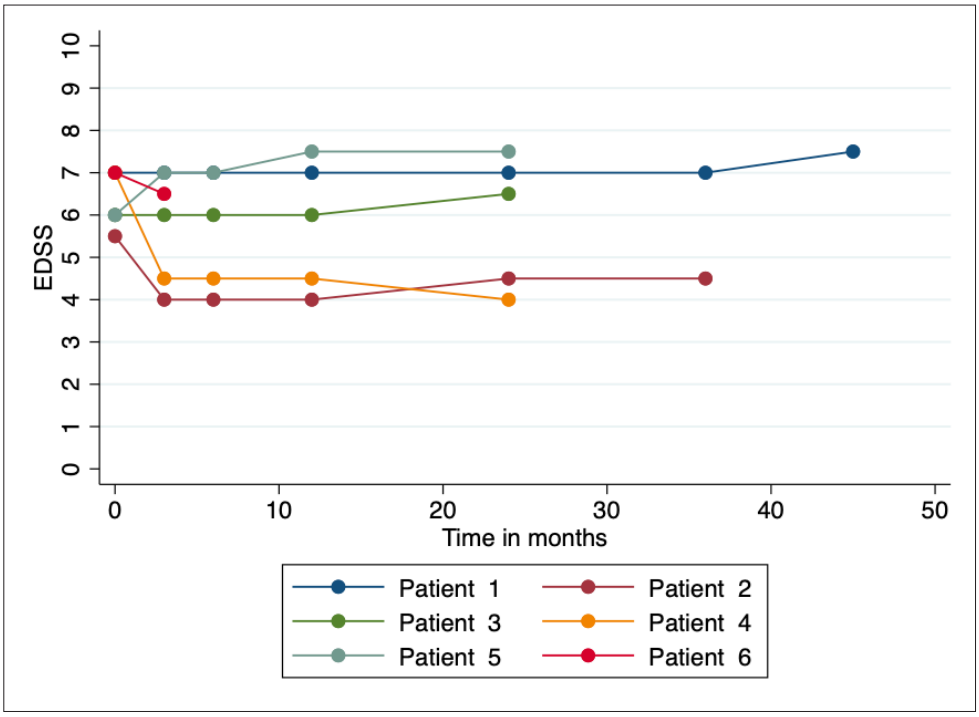

Fig. 1. Dynamics of EDSS after AHSCT.
EDSS, expanded disability status scale; Time 0 is the time of reinfusion of the autologous transplant.

tients with intervals longer than two years and four years, respectively. The decision to perform AHSCT in our patients was based not only on the disease progression rate but also on the availability of DMTs and their reimbursement criteria in the Czech Republic[3]. All patients in our case series had either primary progressive or progressive relapsing disease course. Reimbursement of ocrelizumab for primary progressive MS was only available at the end of 2019. Alemtuzumab was considered; however, several studies have confirmed the superiority of AHSCT over alemtuzumab[11-13]. Furthermore, most patients did not fulfill the reimbursement criteria due to high EDSS scores. Although the value of EDSS at the time of the decision to perform the AHSCT may appear high, we focused on the dynamics of disease progression to higher EDSS values and tried to help these patients as quickly as possible. Due to the small number of patients, we cannot draw any clear conclusions; however, studies with larger cohorts of patients are available[8]. Also, the analysis of complications of AHSCT in our patients showed that this therapy was safe. None of the patients developed grade 4 non-hematological toxicity. The median time of engraftment in leukocytes was 8.5 days. The median time of engraftment in platelets was 9.5 days. None of the patients developed sepsis, and all the infections were mild. We observed an allergic reaction probably to DMSO, considered an infrequent complication of AHSCT and can be managed efficiently by interruption of transplant administration for a couple of minutes[14]. There was a different follow-up time because the AHSCT was performed over several years and the last patient underwent AHSCT at the end of 2021. Further experience is necessary, mainly from the safety and benefits point of view of AHSCT, so that this therapeutic approach could expand into clinical practice, mainly for patients with aggressive MS.

CONCLUSION

Our case series shows that AHSCT is a promising therapeutic approach to slow down the rapid progression of clinical disability in MS patients with a good safety profile. However, further studies especially clinical trials are neccessary for extension into clinical practice.

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