

Autologous Hematopoietic Stem Cell Transplantation for the Treatment of Neuromyelitis Optica in Singapore

Koh Yeow Hoay, Pavanni Ratnagopal

Abstract

Introduction: Neuromyelitis optica (NMO) is an inflammatory and demyelinating autoimmune disorder of the central nervous system, characterised by recurrent attacks of the optic neuritis and myelitis¹. Autologous peripheral blood stem cells transplant (auto-HSCT) has been performed for severe multiple sclerosis refractory to standard therapy with increasing frequency. However, experience of auto-HSCT for NMO is still limited. To our knowledge, there were a total of 3 NMO cases that underwent auto-HSCT in Singapore thus far. We aimed therefore to report our experience and the outcomes of auto-HSCT for NMO patients in Singapore.

Methods: From 2002 to 2015, all the NMO patients (n=3) who underwent autologous peripheral blood stem cells transplant were included in this study. These patients were followed up for 4 to 13 years post-transplantation. Clinical outcomes were monitored using Kurtzke Expanded Disability Status Scale (EDSS) and adverse events following autologous peripheral blood stem cells transplant were observed.

Results: All 3 patients showed lower Kurtzke Expanded Disability Status Scale (EDSS) following autologous peripheral blood stem cells transplant. Two out of 3 patients showed Relapse-Free Survival (RFS), while all 3 patients showed Progression-Free Survival (PFS) following autologous peripheral blood stem cells transplant. No mortality or life-threatening adverse events were observed in all these cases.

Conclusion: All 3 NMO patients in our study showed favourable outcomes following autologous hematopoietic stem cells transplant. Auto-HSCT can be considered as an alternative for NMO patients refractory to conventional treatment.

Keywords: Autologous peripheral blood stem cell transplantation, clinical outcome, neuromyelitis optica, Singapore

Acta Neurol Taiwan 2018;27:26-32

INTRODUCTION

Neuromyelitis optica (NMO), also known as Devic's

disease, is an inflammatory and demyelinating autoimmune disorder of the central nervous system, characterised by recurrent attacks of the optic neuritis and myelitis.¹ The

From the Department of Neurology, National Neuroscience Institute of Singapore, Singapore General Hospital, Singapore.
Received October 1, 2015. Revised November 23, 2015.
Accepted June 21, 2018.

natural history of NMO can be rapidly disabling, resulting in poor quality of life. Immunosuppressive therapy is the first-line treatment for NMO.² However, some patients are either refractory or relapse soon after initial response, posing a challenge for neurologists in managing the disease. New treatment options need to be explored, especially for refractory cases or NMO patients with frequent relapses.

The recent European study showed that autologous hematopoietic stem cell transplantation (auto-HSCT) allows for temporary control of the disease in NMO patients who were highly resistant to conventional treatment, despite a tendency to progress or relapse in the long term.³ Autologous peripheral blood stem cell transplant may theoretically be offered to patients with refractory autoimmune diseases.⁴ Even though preclinical data supports this hypothesis, clinical data about auto-HSCT for NMO is limited, especially in Asian countries as the disease is rare and auto-HSCT is widely available in many Asian countries.

So far, a total of 3 NMO patients have undergone auto-HSCT in Singapore from 2002 to 2015. Herewith, we report our investigational experience with autologous hematopoietic stem cell transplant in 3 patients with NMO in Singapore.

PATIENTS AND METHODS

Patient:

NMO #1 is a 23-year-old Malay lady who presented with recurrent transverse myelitis since 2005. She had a total of 7 relapses of transverse myelitis from 2005 to 2009. She did not complain of any eye symptoms, but her visual evoked potential (VEP) showed bilateral prolonged P100 latencies. She presented with spastic paraparesis with cerebellar ataxia. Her MRI brain scan done in 2009 showed high T2 signal in the right cerebellum and atrophy of both optic nerves (Image 1.0). MRI cervical done in the same year show longitudinal extensive transverse myelitis from C1 to T4 (Image 1.1). Anti-Aquaporin-4 antibody was positive.

She underwent autologous peripheral blood stem cells transplantation (auto-HSCT) in 2010. Pre-transplant Kurtzke Expanded Disability Status Scale (EDSS) was 6.5. After the transplant, she was still having recurrent

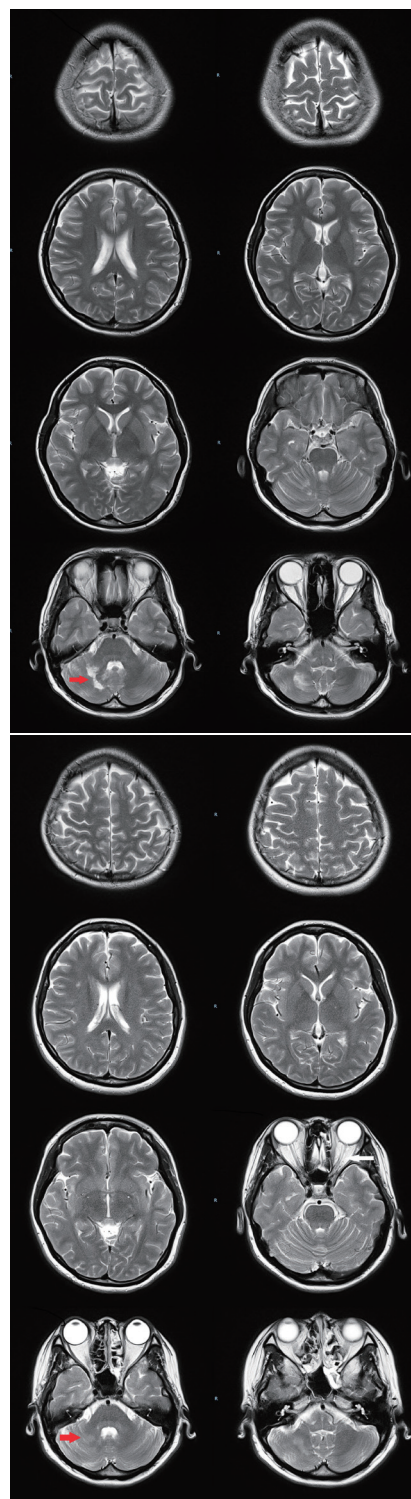


Image 1.0 (left image): MRI brain in 2009 showed high T2 signal in the right cerebellum (red arrow).

Image 1.2 (right image): The MRI brain in 2015 showed improvement of T2 signal intensity in the right cerebellum (red arrow).

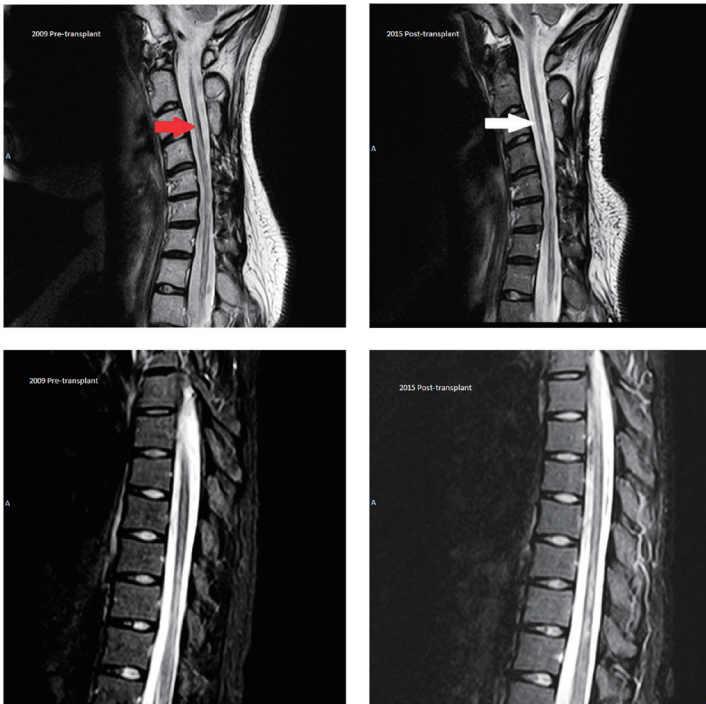


Image 1.1: (MRI cervical spine pre- and post-transplant showed stable T2 hyperintensities extending from C2 to T4.

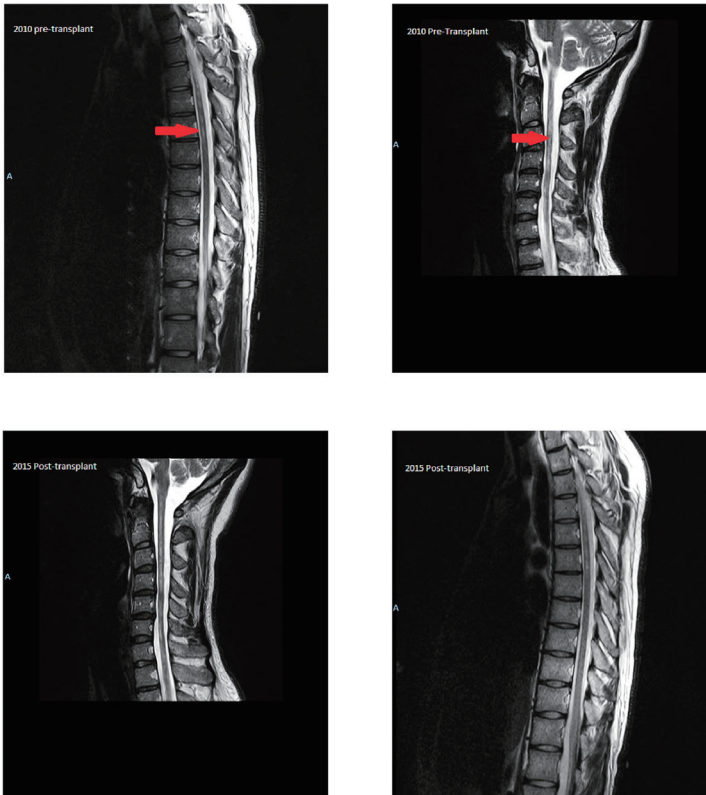


Image 2.0: MRI cervical spine in 2010 (pre-transplant) showed diffused T2 weighted signals in the cervical and upper thoracic cord. Follow-up MRI spine done in 2015 (post-transplant) showed similar cervical and upper thoracic T2 hyperintensity.

attacks of transverse myelitis (4 attacks in 5 years). Nevertheless, her EDSS improved to 4.0 in 2012, then 3.0 in 2013, and remained stable from 2013 to 2015. She had her surveillance MRI brain and cervical spine done in 2015. The MRI brain showed improvement of T2 signal intensity in the right cerebellum (Image 1.2). The MRI cervical spine showed stable T2 hyperintensities extending from C2 to T4. (Image 1.1)

NMO #2 is a 35-year-old Chinese male affected by recurrent optic neuritis and transverse myelitis since 2001. He was initially diagnosed with Relapsing-Remitting Multiple Sclerosis (RRMS), and was treated with interferon from 2007 to 2011. His MRI cervical spine in 2010 showed diffused T2 weighted signals in the cervical and upper thoracic cord (Image 2.0). His Anti-Aquaporin-4 antibody was positive. He underwent auto-HSCT in 2011. At the time of transplantation, his Expanded Disability Status Scale (EDSS) was 3.5. After the transplantation, his EDSS score improved to 3.0 in 2013, then 2.0 from 2014 to 2015. He had a follow-up MRI spine done in 2015. It showed similar cervical and upper thoracic T2 hyperintensity. He has no further relapse after the auto-HSCT.

NMO #3 is a 37-year-old Chinese lady with optic neuritis and longitudinal extensive transverse myelitis, diagnosed in 2000. Her MRI cervical done in 2002 showed area of high T2 signal intensity seen in the cord from C2 to C4 (Image 3.0). She had a total of 4 relapses before the auto-HSCT, requiring IV methylprednisolone. She was not tested for Anti-Aquaporin-4 antibody. However, she fulfilled 2015 International Consensus Diagnostic Criteria

for Neuromyelitis Optica Spectrum Disease (NMOSD).⁵

She underwent autologous hematopoietic stem cell transplantation in 2002. Her pre-transplantation EDSS score in 2002 was 3.0. Her condition improved after auto-HSCT, and her EDSS remains at 1.0 from 2003 to 2015. She had a repeat MRI cervical spine done in 2010 (Image 3.0). The cervical spine MRI showed area of the T2 prolongation in the C2 to C4 spinal cord was smaller, with no overt spinal cord atrophy. She did not have any further relapse after auto-HSCT.

METHODS

From 2002 to 2015, a total of 3 patients with neuromyelitis optica (NMO), diagnosed at the Department of Neurology, Singapore General Hospital, according to 2015 International Consensus Diagnostic Criteria for Neuromyelitis Optica Spectrum Disease (NMOSD) 5, were included in this study.

These 3 patients received the same autologous hematopoietic stem cell transplantation (auto-HSCT) protocol. Peripheral blood stem cells were mobilised with intravenous Cyclophosphamide ($2\text{g}/\text{m}^2$) and subcutaneous granulocyte colony stimulating factor. The conditioning regimen includes intravenous Cyclophosphamide ($200\text{mg}/\text{kg}$) and intravenous Fludarabine ($120\text{mg}/\text{kg}$) given in four equal fractions ($50\text{mg}/\text{kg}$ for Cyclophosphamide and $30\text{mg}/\text{kg}$ for Fludarabine) on Day -5 to Day -2. Stem cells were infused on Day 0.

Clinical outcomes were monitored using the Kurtzke Expanded Disability Status Scale (EDSS). Adverse

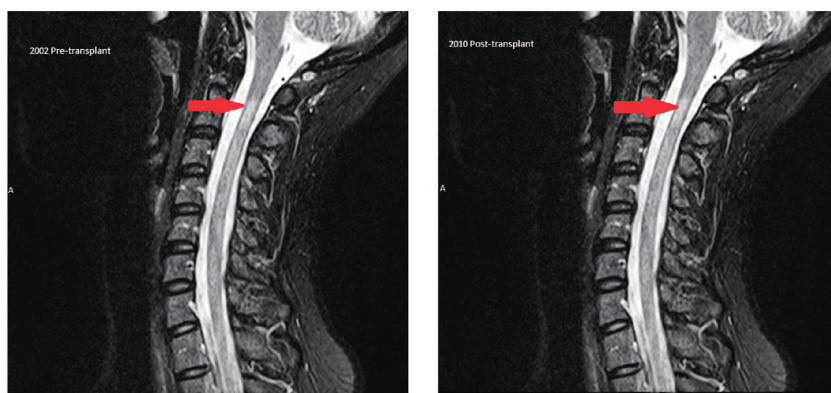


Image 3.0: MRI cervical in 2002 (pre-transplant) showed area of high T2 signal intensity seen in C2 to C4. Surveillance MRI cervical spine done in 2010 (post-transplant) showed smaller C2 to C4 T2 cord signal (arrow).

events (pre- and post- auto-HSCT) were reviewed during hospitalisation and follow-up. Follow-up MRI brain and MRI whole spines were performed for all 3 patients post-auto-HSCT, but Anti-Aquaporin-4 antibody test was not performed post-auto-HSCT.

RESULT

3.1 Neurological Assessment following Auto-HSCT

After a median follow-up of 7.3 years (4-13 years), 2 out of 3 have Relapse-Free Survival (RFS), defined as survival without evidence of disease activation, either clinically by the occurrence of acute disease exacerbation or of disease relapse.

All 3 patients achieved Progression-Free Survival (PFS). PFS was calculated as survival without progression, defined as worsening of neurologic disability beyond the pre-treatment baseline. Worsening was defined as an increase of at least one point of EDSS score for patients with a pre-transplant baseline EDSS score of ≤ 5 or an increase of at least 0.5 point in EDSS score for patients with baseline EDSS score of >5 . Functional outcomes

before and after auto-HSCT are shown in Figure 1. It shows reduced or stable EDSS following Auto-HSCT.

In summary, all 3 patients were neurologically stable with no progression in their EDSS scores, or development of new lesions on their follow-up MRI.

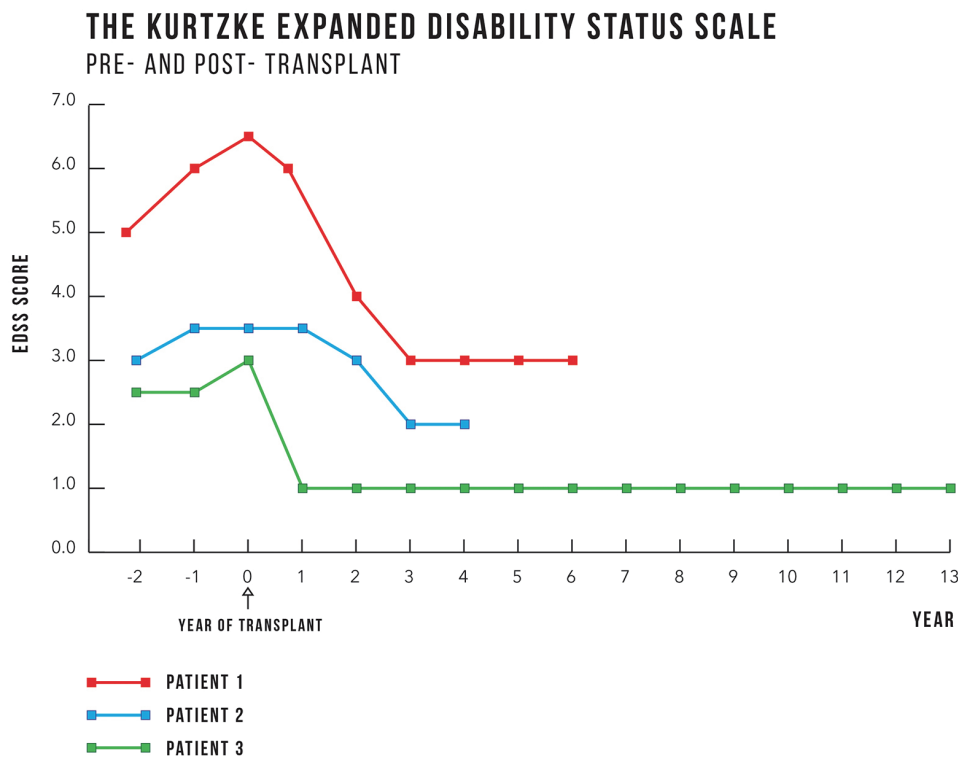
3.2 Adverse Events following APBST

All adverse reactions (AEs) were defined according to Common Toxicity Criteria version 4.0 (CTC reference: <http://ctep.cancer.gov/reporting/ctc.html>).

There was no mortality reported in all the 3 cases. One of the cases reported having febrile neutropenia after the transplant. No secondary autoimmune disease or secondary malignancies were observed.

DISCUSSION

Autologous hematopoietic stem cell transplant (auto-HSCT) has been proposed as a therapeutic option for patients with severe refractory multiple sclerosis⁶. In contrast to multiple sclerosis, the roles of auto-HSCT in neuromyelitis optica (NMO) are still unclear as



NMO attacks are predominantly mediated by B cells and antibody response, instead of by T-cells-mediated. Therefore, humoral immunity, including complement activation, plays an important role in their pathogenesis^{7,8}. Since auto-HSCT mainly eradicates the auto-reactive T cells using high-dose chemotherapy, it may be less effective for B-cell mediated autoimmune conditions⁹.

Data about auto-HSCT for NMO are limited. The first available data regarding auto-HSCT for NMO comes from a Chinese study of 21 cases of opticospinal NMO patients⁶ and a few other case reports.¹⁰ In view of the favourable results from these studies, the European Group for Blood and Marrow Transplantation (EBMT) guidelines classified auto-HSCT as an ‘amendable clinical option’ for refractory NMO.¹¹ Subsequently, the registry study of the EBMT Autoimmune Diseases Working Party illustrated for the first time that auto-HSCT can effectively be used to stabilise NMO, at least in the short term with a low side effect profile.³

In our study, these 3 patients were initially diagnosed as refractory multiple sclerosis (refractory MS). They were offered auto-HSCT because of ‘refractory MS’. The diagnosis of NMO only made after the transplantation when Aquaporin-4 antibody tests were more widely available, and clinical diagnosis of NMO can be made more easily with the new diagnostic criteria. Surprisingly, the retrospective data collected from these 3 refractory NMO patients showed favourable outcomes. In addition, there was no life-threatening adverse event seen.

The exact mechanisms accounting for the role of auto-HSCT is still unknown. Several mechanisms may have contributed to the effect of auto-HSCT in NMO. These include B-cell depletion¹² with subsequently reduced inflammatory response, elimination of memory B cells after auto-HSCT, and seroconversion of Aquaporin-4 antibody (seen in a few case reports¹³).

The limitation of our study is the limited number of patients and the retrospective nature of this study. It is difficult to compare the definitive role of auto-HSCT with other alternative options (Rituximab, allogenic bone marrow transplantation, or other new immunosuppressive therapies). In addition, Aquaporin-4 antibody serostatus was not tested after the transplant in this study.

In conclusion, our study showed favourable outcomes for auto-HSCT in refractory NMO patients in Singapore.

It allows disease stabilisation with a low toxicity profile. However, more data is needed to validate the role of auto-HSCT in refractory NMO patients. Nevertheless, treatment specially targeting B-cells, such as monoclonal antibody to CD20 (Rituximab), may be more effective to NMO patients than auto-HSCT.¹⁴

REFERENCE

1. Sellner J, Boggild M, Clanet M, et al. EFNS guidelines on diagnosis and management of neuromyelitis optica. *Eur J Neurol* 2010; 17: 1019-1032.
2. Collongues N, de Seze J. Current and future treatment approaches for neuromyelitis optica. *The Adv Neurol Disord* 2011; 4: 111-121.
3. Greco R, Bondanza A, Oliveira MC et al. Autologous stem cell transplantation in neuromyelitis optica: a registry study of the EBMT Autoimmune Diseases Working Party. *Mult Scler*. 2015; 21(2): 189-197.
4. Snowden JA, Saccardi R, Allez M, et al. Haematopoietic SCT in severe autoimmune diseases: Updated guidelines of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant* 2012; 47: 770-790.
5. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*. 2015; 85(2): 177-189.
6. Xu J, Ji BX, Su L, et al. Clinical outcome of autologous peripheral blood stem cell transplantation in opticospinal and conventional multiple sclerosis in Chinese population. *Ann Hematol* 2011; 90: 343-348.
7. Luccinetti CF, Mandler RN, McGavern D et al. A role for the humoral mechanisms in the pathogenesis of Devic’s neuromyelitis optica. *Brain* 2002; 125: 1450-1461.
8. Graber D, Levy M, Kerr D et al, 2008. Neuromyelitis optica pathogenesis and aquaporin 4. *J Neuroinflammation*; 5: 22-42.
9. Roemer SF, Parisi JE, Lennon VA et al, 2007. Pattern-specific loss of aquaporin 4 immunoreactivity distinguishes neuromyelitis optica from multiple sclerosis. *Brain* 130; 1194-1205.
10. Peng F, Qiu W, Li J, et al. A preliminary result of treatment of neuromyelitis optica with autologous

- peripheral blood stem cell transplantation. *Neurologist* 2010;16: 375-378.
11. Snowden JA, Saccardi R, Allez M, et al. Haematopoietic SCT in severe autoimmune diseases: Updated guidelines of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant* 2012; 47: 770-790.
 12. Pittock SJ, Lennon VA, McKeon A, et al. Eculizumab in AQP4-IgG-positive relapsing neuromyelitis optica spectrum disorders: An open-label pilot study. *Lancet Neurol* 2013; 12: 554-562.
 13. Aouad P, Li J, Arthur C et al. Resolution of aquaporin-4 antibodies in a woman with neuromyelitis optica treated with human autologous stem cell transplant. *J Clin Neurosci*. 2015 Jul; 22(7): 1215-7.
 14. Jacob A, Weinschenker BG, Violich I et al, 2008. Treatment of myelitis optica with rituximab. *Arch Neurol*; 65: 1443-1448.