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Blood 142 (2023) 7115–7116

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

732.ALLOGENEIC TRANSPLANTATION: DISEASE RESPONSE AND COMPARATIVE TREATMENT STUDIES

Allogeneic Hematopoietic Stem Cell Transplantation for Adult Metachromatic Leukodystrophy (MLD): A Case Series

Andreas Riedel[1], *Christoph Faul, MD*[2], *Kristina Reuss, MD*[2], *Peter Lang, MD PhD*[3], *Claudia Lengerke, MD*[2], *Nadine Weissert, MD*[4], *Holger Hengel*[4], *Ludger Schoels, MD*[4], *Wolfgang Andreas Bethge, MD*[2]

[1] Department of Internal Medicine II, Hematology, Oncology, Clinical Immunology and Rheumatology, University Hospital Tuebingen, Stuttgart, Germany
[2] Department of Internal Medicine II, Hematology, Oncology, Clinical Immunology and Rheumatology, University Hospital Tuebingen, Tuebingen, Germany
[3] Dpt. I - General Pediatrics, Hematology and Oncology, University Children's Hospital Tübingen, Tübingen, Germany
[4] Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE), University Hospital Tuebingen, Tuebingen, Germany

Introduction
Adult Metachromatic Leukodystrophy (MLD) is a rare neurological disorder leading to devastating and progressive cognitive impairment and motor impairment with ataxia, spasticity and neuropathy as well as incontinence resulting in complete disability and reduced life expectancy. MLD is caused by autosomal recessive mutations of the ARSA gene, resulting in reduced arylsulfatase A enzyme (ARSA) activity and consecutive accumulation of galactosylceramide-3-0-sulfate in the central nervous system (CNS). Potential therapies in infantile and juvenile MLD include allogeneic hematopoietic stem cell transplantation (allo-HCT), ex-vivo gene therapy (Atidarsagen autotemcel), and (intrathecal) enzyme replacement as tested in ongoing trials. Allo-HCT may slow down or stop MLD progression. However, the outcome in adult patients treated with allo-HCT has been only reported in a few case reports. In this case series, we report our experience of allogeneic transplantation in four patients with adult MLD.
Methods
Four patients (2 male and 2 female) with a genetically confirmed diagnosis of adult MLD, with enzyme deficiency detectable in peripheral blood (ARSA activity range 0.00-0.06 E514nm/10 $^{-6}$), evidence of white matter lesions on MRI and demyelinating polyneuropathy in EMG were treated with allo-HCT. One patient was still clinically asymptomatic at the treatment timepoint. Allo-HCT was performed at an age between 18 and 37 years (mean 25.75 years) and within one year after diagnosis. Bone marrow (n=2) or mobilized peripheral blood stem cells (n=2) from 10/10 matched related (n=1) or unrelated (n=3) donors were infused at a dose of 2.2-7.82x10 ^{6} CD34+/kg after a reduced intensity conditioning regime with Fludarabine (150 mg/m²) and Treosulfane (10 or 14 g/m²). Three patients received further infusions with allogeneic mesenchymal stem cells (MSCs) manufactured in the hospital´s own GMP laboratory around day 30 after transplantation. One patient received a second MSC infusion at day 182. MSCs are able to secrete ARSA and were used to consolidate enzyme levels.
In case of transplant failure donor lymphocytes (DLI) were given. For posttransplant immunosuppression Tacrolimus, Methotrexate, Mycophenolate mofetil or Anti-thymocyte globulin (ATG, Grafalon®, Neovii 10 mg/kg) were used.
Results
All patients engrafted 16-21 days after HCT. Platelets regenerated within 14 to 21 days (mean 16 days), neutrophils recovered within 16 to 21 days (mean 18.5 days). In two patients hepatitis and exanthema associated with ATG administration were observed as transient adverse events. Other therapy-associated adverse events were innappetence, hyperkalemia and diarrhea. A mild Graft-versus-host disease of the skin occurred only in one patient with full resolution on a course of steroids and Tacrolimus. After allo-HCT, an increase in ARSA levels reaching normal range values within the first 12 months after treatment was already documented in 3 out of 4 patients; measurements are pending in the 4 th more recently transplanted patient. Three out of four patients developed consistent full donor chimerism within 11 (1-11) months after HCT. In the fourth 18-year-old patient autologous chimerism increased to 60-80%, while ARSA activity decreased from 1.05 to 0.61 E514nm/10 $^{-6}$. Consequently, the patient received DLIs. However, an improvement in chimerism has not be achieved so far. Longer follow-up data will be reported at the meeting.
Discussion and Conclusion

Allo-HCT in patients with MLD can be used to restore normal range ARSA activity. Donor-derived macrophages with an adequate secretion of ARSA migrate to the central nervous system and release ARSA. To our knowledge, there have been only a few individual case reports on allo-HCT in adult MLD so far. Our case series indicates that allo-HCT can be performed with tolerable risks and evident efficacy in adult patients with MLD. Based on this experience and previously reported cohorts in juvenile and infantile MLD allo-HCT should be thus also considered as a therapeutic option for adult patients with MLD. Longer clinical follow-up, higher patient numbers and ultimately a prospective randomised trial containing an untreated group would be needed to evaluate allo-HCT as a treatment option for adult MLD.

Disclosures No relevant conflicts of interest to declare.

https://doi.org/10.1182/blood-2023-187317