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Hematopoietic Cell Transplantation for MPS Patients Is Safe and Effective: Results after Implementation of International Guidelines

Mieke Aldenhoven [1], Simon A. Jones [2], Denise Bonney [3], Roisin E. Borrill [3], Mary Coussons [3], Jean Mercer [2], Marc Bierings [1], Birgitta Versluys [1], Peter M. van Hasselt [4], Frits A. Wijburg [5], Ans T. van der Ploeg [6], Robert F. Wynn [7], ***Jaap Boelens*** *[1]. [1] Pediatric Blood and Marrow Transplantation Program, University Medical Center Utrecht, Utrecht, Netherlands; [2] Willink Unit, Manchester Centre for Genomic Medicine, CMFT, University of Manchester, Manchester, United Kingdom; [3] Blood and Marrow Transplant Unit, Royal Manchester Children's Hospital, Manchester, United Kingdom; [4] Department of Metabolic Disorders, University Medical Center Utrecht, Utrecht, Netherlands; [5] Department of Pediatrics and Amsterdam Lysosome Centre 'Sphinx', University of Amsterdam, Amsterdam, Netherlands; [6] Center for Lysosomal and Metabolic Diseases, Erasmus MC University Medical Center, Rotterdam, Netherlands; [7] Royal Manchester Children's Hospital, Manchester, United Kingdom*

Background: Allogeneic hematopoietic cell transplantation (HCT) is the only treatment option able to prevent progressive neurodegenerative disease in a selected group of mucopolysaccharidoses (MPS) disorders. However, its use was historically limited by the high risk of graft failure and HCT-related morbidity and mortality. Therefore in 2005, the European Blood and Marrow Transplantation group developed transplantation guidelines for HCT in MPS patients. We prospectively evaluated the outcomes of HCT in MPS patients, complying with these international guidelines in two centers performing the highest numbers of HCT in MPS patients in Europe.

Methods: Two consecutive conditioning regimens were used, either Busulfan/Cyclophosphamide (Bu/Cy) or Fludarabine/Busulfan (Flu/Bu)-based, both with exposure-targeted intravenous Busulfan. A non-carrier matched sibling donor (MSD) or an identical unrelated cord blood (UCB, 6/6 on intermediate resolution) or identical matched unrelated donor (MUD, 10/10 on high-resolution typing) were considered preferred donors. If not available, a mismatched UCB donor was used.

Results: 62 MPS patients were included (56 MPS type I – Hurler, 2 MPS type II, 2 MPS type III, and 2 MPS type VI); 29 receiving a BuCy, 33 a FluBu-based conditioning regimen. Median age at HCT was 13.5 (range 3-44) months. 41 patients received an UCB donor, 17 a MSD, and 4 a MUD. High overall survival (95.2%) and event-free survival (90.3%) were achieved (Figure 1). All three patients with graft failure received a second HCT and are alive and with successful donor engraftment at latest follow-up. A mismatched donor predicted for lower event-free survival ($p=0.04$). The probability of aGVHD grade II-IV was 13.3%, while 14.8% of the patients were diagnosed with cGVHD (1.9% extensive). A higher age at HCT was a predictor for both aGVHD ($p=0.001$) and cGVHD ($p=0.01$). The use of a mismatched donor was a predictor for aGVHD ($p=0.01$). Full-donor chimerism and normal enzyme levels were found in 88.2% and 95.1% of the patients, respectively. Higher rates of full-donor chimerism were achieved in UCB recipients ($p=0.002$).

Conclusion: If complying with the international HCT guidelines, HCT in MPS patients results in high safety and efficacy. This allows extension of HCT to more attenuated MPS types such as MPS type I – Hurler-Scheie. As a younger age at HCT is associated with reduction of HCT-related toxicity, newborn screening may further increase safety.

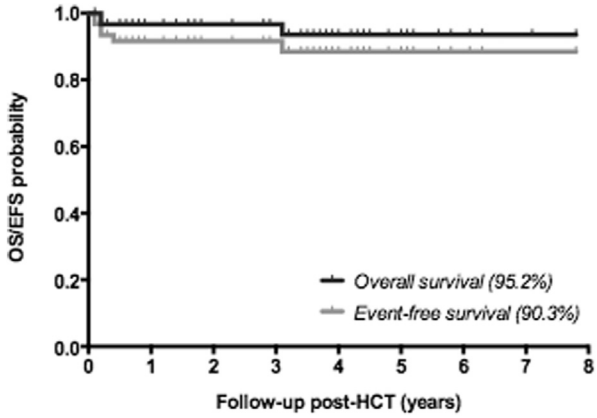

Figure 1. Overall survival (OS) and event-free survival (EFS).

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Combining Clofarabine/Fludarabine with Exposure Targeted Busulfan for Pediatric Leukemia: An Effective, Low Toxic TBI-Free Conditioning Regimen

Jaap Boelens *[1], Robbert Bredius [2], Birgitta Versluys [1], Wouter Kollen [3], Caroline A. Lindemans [1], Arjan Lankester [4], Marc Bierings [1]. [1] Pediatric Blood and Marrow Transplantation Program, University Medical Center Utrecht, Utrecht, Netherlands; [2] Leiden University Medical Center, Leiden, Netherlands; [3] Pediatric Blood and Marrow Transplantation Program, LUMC, Leiden, Netherlands; [4] Department of Pediatrics, Leiden University Medical Center, Leiden, Netherlands*

Background: The combination of Clofarabine + Fludarabine + Busulfan (CloFluBu) was found to have synergistic anti-leukemic activity against ALL and AML blasts *in vitro* (Andersson et al: BBMT 2011). As TBI induces significant late effects in childhood ALL, and AML patients have high relapse rates, we hypothesized that CloFluBu may be an interesting alternative to TBI in ALL and add anti-leukemic activity in AML. Within the "Dutch COG HCT Working Group" we prospectively studied the outcomes of CloFluBu-conditioning regimen for lymphoblastic and myeloid malignancies.

Methods: Patients from the 2 pediatric HCT programs (LUMC and UMC Utrecht) with a lymphoblastic or myeloid malignancy were included from Aug-2011 to present. Clofarabine 30mg/m^2 was given in 1 hour, followed by Fludarabine 10mg/m^2 in 1 hour followed by a 3-hour infusion of once daily targeted busulfan (weight-based dosing: with therapeutic drug monitoring). Thymoglobulin was added in unrelated donors (except in AML patients receiving cord blood: CB) and GvHD prophylaxis was according to standard protocols. The cumulative target area under the curve (AUC) for Bu was 90 mg*h/L. Primary endpoint: leukemia free survival (LFS) and overall survival (OS). Other endpoints: acute and chronic graft-versus-host disease (GvHD), VOD, non-infectious lung injury, neutrophil (@day60) and thrombocyte engraftment (@day 180). A predictor analysis was performed using Cox Proportional Hazard Models.

Results: 62 patients were included: 28 AML-CR2, 14 ALL-CR1, 3 Infant-ALL, 11 ALL-CR2/3, 6 other (4 MDS, 2 CML, 1CNL). 10/19 ALL-CR1-3 patients with available MRD status prior to HCT were positive: 4 >10e-3 and 6 < 10e-3. Donors used: 25 unrelated CB, 14 (matched) Family donors (FD; 1 Haploidentical) and 23 Matched Unrelated Donors. Median age at HCT: 10.9 (0.5-17.9) years. Median follow-up 298 (range 18-1182) days. The estimated 2-year OS/LFS was 74+/-7%