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

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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.

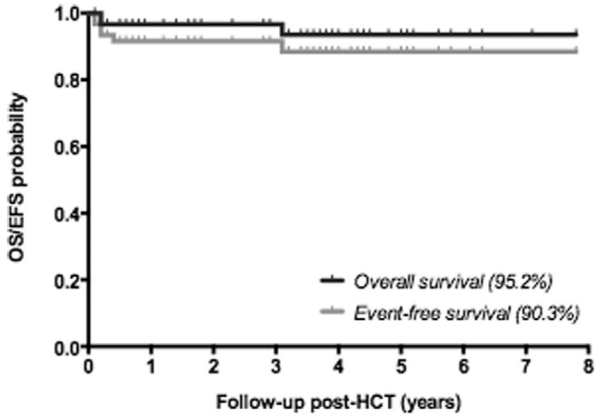

Figure 1. Overall survival (OS) and event-free survival (EFS).

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

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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%

(AML 76%, ALL-CR1 100%, MDS 67%, ALL-CR2-3 59%), with an estimated NRM@1year of 9+/-4% and relapse@1year of 21+/-7%. Other endpoints: Probability of neutrophil engraftment 100% @day60 and thrombocyte engraftment (50x10e9/L) of 84+/-6% @day 180, only 1 graft failure (1.5%: MUD donor. Successfully re-grafted with CB) was noted. Toxicity endpoints: aGvHD 2-4 @day 180 was 32+/-6% (grade 3-4: 14+-4%), extensive cGvHD@1year 8+-6%, non-infectious lung-injury @ 2 years 12+-4% and no VOD (0%) was noted.

Conclusion: The preliminary results of this TBI-free conditioning regimen (CloFluBu) in myeloid- and lymphoblastic malignancies showed limited toxicity and encouraging LFS given the high risk group of patients. A longer follow-up and a larger cohort is needed to draw firm conclusions with regards to the anti-leukemic effect and late effects.

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Excellent Outcome for Fanconi Anemia Patients Undergoing Hematopoietic Stem Cell Transplantation (HSCT) without Radiation: A Single Center Experience on 103 Patients

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Fanconi anemia(FA) is a rare genetic disorder characterized by congenital defects, bone marrow failure and cancer predisposition. Over the past decade, survival after HSCT has greatly improved and the use of protocols without radiation are preferred in order to decrease late complications related to the development of head and neck cancer. In this study we analyzed 103 patients(pts) with FA who were transplanted between 2003 and 2014. The median age at HSCT was 9ys(range: 3-23ys). All pts were transplanted in marrow failure and received bone marrow from matched siblings (MSD) (n=49) or Alternative donors (AD) (n=54). This latter group included 12 other related donors(ORD) and 42 unrelated donors(URD). Preparatory regimen with Cyclophosphamide 60mg/kg(CY60) was given to all pts with MSD or ORD while pts with URD received CY60 + Fludarabine 125mg/m2 + rabbit ATG 5mg/kg. All pts received GVHD prophylaxis with cyclosporine and methotrexate. Three pts died before D+28 and were not evaluable for engraftment (MSD: 2 pts and URD: 1 pt). One patient (MSD) developed primary graft failure, received a 2nd transplant without success and was finally rescued after a 3rd transplant with a haploidentical donor. She is alive and well 3ys after HSCT. Ninety-nine pts engrafted but 5 pts developed late graft failure (MSD=2pts; ORD=1pt; URD=1pt) between 50 and 742 days after transplant (M: 84 days). Four out of these 5 pts are alive and well with full donor chimerism after a 2nd or 3rd HSCT. At last follow-up, the majority of pts transplanted from AD had full donor chimerism (96%) while approximately 50% of pts with MSD donors had mixed chimerism. Mucositis grade II-III occurred in 70% of pts. Viral infections were more frequent when AD were used(60%) compared to MSD(28%). Hemorrhagic cystitis occurred in 22% of AD transplants and it was uncommon after MSD transplants (only 1 pt). After AD transplantation, acute GVHD grade II-IV occurred in 12/53 evaluable pts and any Chronic GVHD occurred in 21/38 evaluable pts. MSD had a lower incidence of acute GVHD (3/47 evaluable pts) while Chronic GVHD occurred in 14/47 evaluable pts. Ninety-one pts are alive between 7 months and 10 years (M: 5 yrs) with an overall survival of 87% at 5 years. There was no difference in survival according to the type of donor MSD (92%), ORD (92%) and URD(83%). Patients without Acute GVHD had an overall survival of 98% compared to 58% with acute GVHD (p:0.001). Twelve pts died between 3 and 1855 days after HSCT(M:65 days). Acute or chronic GVHD were the major causes of death (n=8) followed by infections (n=3) and central nervous system bleeding (n=1).

Conclusions: HSCT for FA has improved dramatically during the past decade. In this study, the use of non-irradiation protocols was associated with an excellent survival, successful engraftment and very low mortality rate.

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Infusion of Ex Vivo Expanded Cord Blood Progenitor Cells Is Associated with Reduced Hospital Days and Utilization of Opiate Infusion and Total Parenteral Nutrition in Patients Receiving Myeloablative Cord Blood Transplantation

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Background: Cord blood transplant (CBT) recipients have delayed hematopoietic recovery compared to recipients of other stem cell sources following allogeneic transplant. Prolonged neutrophil (ANC) recovery, in particular, places these patients at risk of protracted mucositis, extended hospitalization and increased risk of infection-related morbidity and mortality. To mitigate these risks, we have developed a methodology for generating increased absolute numbers of cord blood (CB) hematopoietic stem/progenitor cells (HSPC) by culture of the CB HSPC in the presence of Notch ligand, cryopreserving the final harvested product, and subsequently administering the product as an adjunct cellular therapy to patients receiving CBT. This has resulted in significantly decreased time to neutrophil recovery following CBT[1]. Here we evaluated whether administration of these cells impacted duration of hospitalization, use of opiate pain medications, and requirement for total parenteral nutrition (TPN) or infectious outcomes during initial hospitalization for CBT.

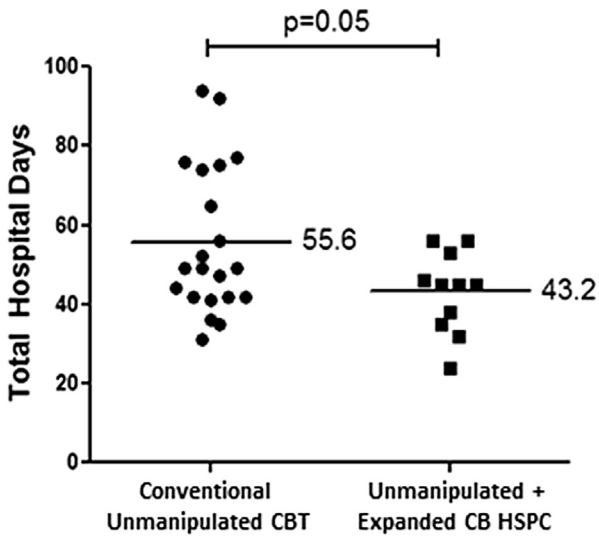

Figure 1. Overall survival (OS) and event-free survival (EFS).