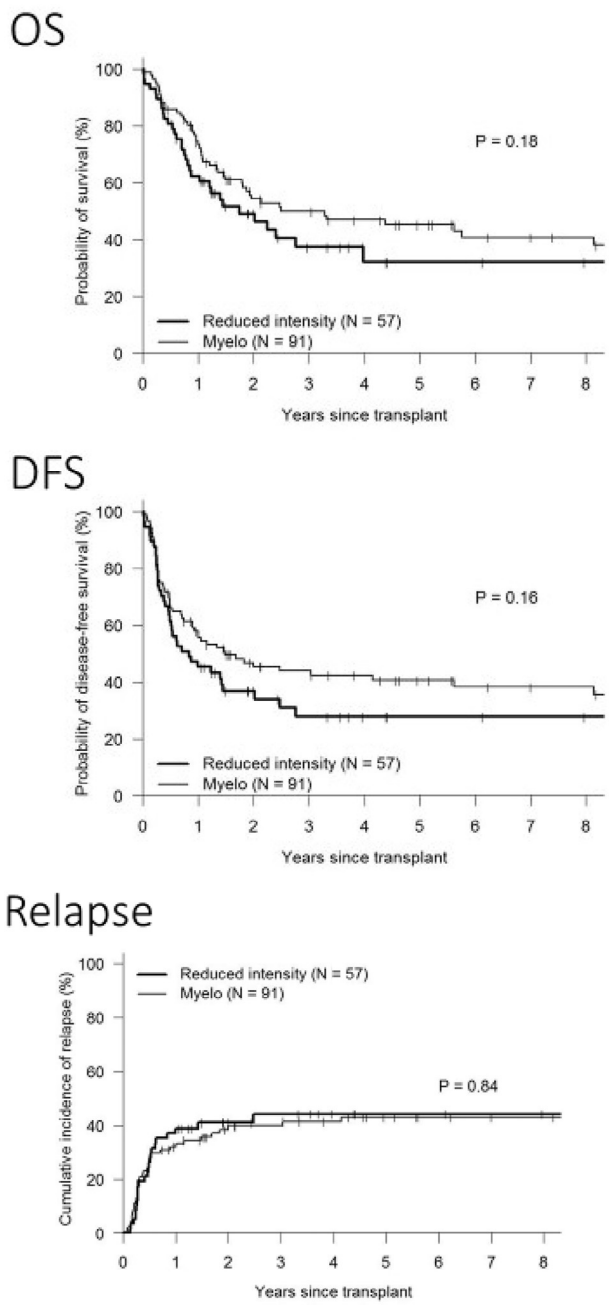

Figure 1. Adjusted K-M estimates for OS, DFS and Relapse among high/very high DRI risk group.

impact on OS, DFS, NRM or relapse among high/very high DRI AML and MDS patients whereas for low/intermediate DRI, MA conditioning was associated with better DFS (HR .58, 95% CI .39-0.88, $P = .01$), lower relapse (HR .56, 95% CI .32-0.97, $P = .038$) and similar NRM (HR1.11, 95% CI .54-2.26, $P = .781$) compared to RIC.

MA does not improve survival or disease control among AML and MDS patients with high/very high DRI risk. Using less toxic upfront RIC followed by post-transplant consolidative strategies for patients with high/very high DRI might prove to be more successful at improving the outcomes of these patients.

69

High Treosulfan Exposure is Associated with Early Toxicity in Pediatric Hematopoietic Stem Cell Transplantation: A Prospective Multicenter Study

Eileen van der Stoep [1], *Alice Bertaina* [2], *Marloes ten Brink* [1], *Robbert Bredius* [3], *Frans Smiers* [3], *Dominique Wanders* [3], *Dirk Jan Moes* [1], *Franco Locatelli* [2], *Henk-Jan Guchelaar* [1], *Juliëtte Zwaveling* [1], *Arjan Lankester* [3]. [1] *Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, Netherlands;* [2] *Department of Pediatric Hematology/Oncology, Bambino Gesù Children's Hospital, University of Pavia, Rome, Pavia, Italy;* [3] *Department of Pediatrics, Leiden University Medical Center, Leiden, Netherlands*

Treosulfan-based conditioning is increasingly used in pediatric hematopoietic stem cell transplantation (HSCT) due to its potent immunosuppressive and cytotoxic efficacy combined with a favorable toxicity profile. Data on treosulfan pharmacokinetics in children are limited, and the relationship between treosulfan exposure, toxicity and clinical outcome is unresolved.

In this multicenter prospective observational study, we studied treosulfan pharmacokinetics and the relation with

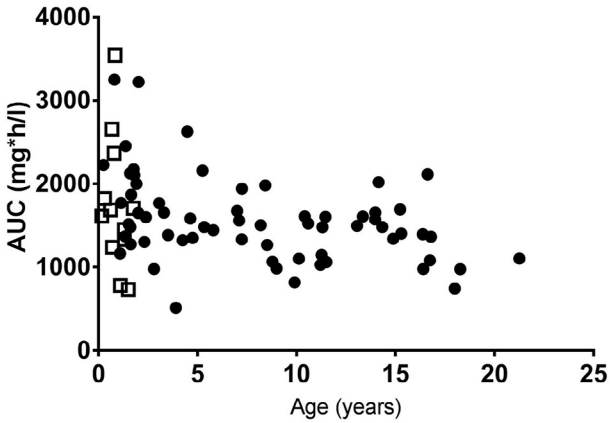

Figure 1. The relation between treosulfan exposure and age. The vertical axis represents the Area under the Curve (AUC) values in mg*hr/L. Symbols represent the different dosing schemes: 14 g/m^2 (●), 10 g/m^2 (□).

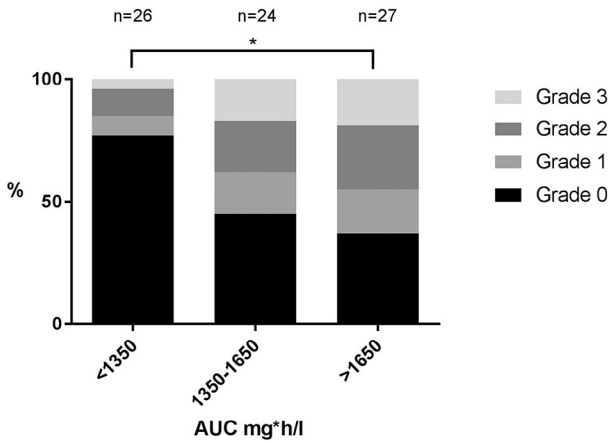

Figure 2. Incidence of mucositis in different treosulfan exposure groups. The incidence of mucositis is shown according to grade, with black being grade 0, progressing to light gray being grade 3. (*Grade 0/1 vs grade 2/3, $P = .026$).

regimen-related toxicity and early clinical outcome in 77 pediatric patients (median age 4.6 years; range .2-21.3). Patients transplanted in the pediatric transplant units in Leiden and Rome between June 2011 and July 2016 receiving a conditioning regimen with treosulfan combined with fludarabine or fludarabine and thiotepa for malignant and non-malignant indications were included. Treosulfan dose was 3x10 g/m^2 in infants <1 year old (n = 12), and 3x14 g/m^2 in children ≥1 year old (n = 65), respectively. Mean day 1 treosulfan exposure was 1, 744 ± 795 mg*hr/L (10 g/m^2) and 1, 561 ± 511 mg*hr/L (14 g/m^2), with an inter-individual variability of 56 and 33%, respectively. Treosulfan clearance was lower in children <1 year old (2.15 vs. 7.82 ml/min/kg, $P < .001$). High treosulfan exposure (>1, 650 mg*hr/L) was associated with an increased risk of mucosal (OR 4.40; 95%CI 1.19-16.28, $P = .026$) and skin toxicity (OR 4.51; 95%CI 1.07-18.93, $P = .040$) compared to exposure under 1350 mg*hr/L. Also, the risk of experiencing multiple toxicities (i.e. mucositis, skin and/or liver toxicity) is higher when treosulfan exposure exceeds 1650 mg*hr/L (OR 4.52; 95% CI 1.32-15.53, $P = .016$). No correlation was found between treosulfan exposure and the early clinical outcome parameters engraftment, acute graft-versus-host disease (≥grade 2), and donor chimerism at day +30, +100 and 1 year.

Our study is the first to provide for high variability in treosulfan pharmacokinetics and an association between treosulfan exposure and early toxicity in a large cohort of pediatric patients. Ongoing studies will provide further evidence if treosulfan exposure is related to long-term disease-specific outcome and late toxicities.

70

Role of Anti-Lymphocyte Globulin in Prophylaxis of Graft-Versus-Host Disease after Allogeneic Stem Cell Transplantation in Patients with Acute Leukemia

Manabu Wakamatsu [1], *Naoyuki Uchida* [2], *Kazuteru Ohashi* [3], *Takahiro Fukuda* [4], *Heiwa Kanamori* [5], *Yukiyasu Ozawa* [6], *Tatsuo Ichinohe* [7], *Yoshinobu Kanda* [8], *Makoto Murata* [9], *Koji Kato* [1], *Yoshiko Atsuta* [10], *Takanori Teshima* [11].

[1] *Department of Hematology and Oncology, Children's Medical Center, Japanese Red Cross Nagoya First Hospital, Nagoya, Japan;* [2] *Department of Hematology, Toranomon Hospital, Tokyo, Japan;* [3] *Hematology Division, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan;* [4] *National Cancer Center Hospital, Tokyo, Japan;* [5] *Department of Hematology, Kanagawa Cancer Center, Yokohama, Japan;* [6] *Department of Hematology, Japanese Red Cross Nagoya First Hospital, Nagoya, Japan;* [7] *Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan;* [8] *Division of Hematology, Saitama Medical Center, Jichi Medical University, Saitama, Japan;* [9] *Department of Hematology and Oncology, Nagoya University Graduate School of Medicine, Nagoya, Japan;* [10] *Department of Healthcare Administration, Nagoya University Graduate School of Medicine, Nagoya, Japan;* [11] *Department of Hematology, Hokkaido University Faculty of Medicine, Sapporo, Japan*

Background: Because the clinical implication of anti-lymphocyte globulin (ATG/ALG) is not completely understood, we attempted to identify the clinical impact of ATG/ALG in patients with acute leukemia who received allogeneic stem cell transplantation (allo-SCT) in Japan.

Methods: We retrospectively analyzed patients with acute lymphocytic leukemia (ALL; n = 4813) and acute myeloid leukemia (AML; n = 9719) who received allogeneic SCT between 2000 and 2015 with (n = 1355) or without (n = 13177) ATG/ALG as part of the conditioning regimen. The median age was 42 years with a range of 0-80 years. Patients were grouped based on the stem cell sources used, which were bone marrow (BM, n = 7411), cord blood (CB, n = 4309), and peripheral blood (PB, n = 2812). The median total dose of ATG was 2.5 mg/kg in each patient group. Haploidentical donors (HLA ≥ 2 antigen-mismatched family donors, n = 1598) were 492 in the BM group and 1106 in the PB group.

Results: The 3-year overall survival (3 yr-OS) of all patients with and without ATG/ALG was 32.5% vs. 47.1% ($P < .001$), respectively, and multivariate analysis showed that ATG/ALG reduced grade II-IV acute graft-versus-host disease (aGVHD; $P = .019$, HR = 1.121) as well as chronic GVHD (cGVHD; $P < .001$, HR = 1.397), but decreased OS ($P < .001$, HR = 1.180). The 3 yr-OS with and without ATG/ALG was 46.8% vs. 52.7% ($P = .036$) in the BM group, 27.5% vs. 39.4% ($P = .003$) in the CB group, and 23.9% vs. 43.6% ($P < .001$) in the PB group, respectively. Multivariate analysis showed that in the BM group, ATG/ALG significantly reduced grade II-IV aGVHD ($P < .001$, HR = 1.397) and cGVHD ($P = .018$, HR = 1.243); in the CB group, it significantly reduced grade II-IV aGVHD ($P = .015$, HR = 1.484) and cGVHD ($P < .001$, HR = 2.375) but increased treatment-related mortality (TRM; $P = .006$, HR = 1.350) and decreased OS ($P = .009$, HR = 1.282), and in the PB group, it significantly reduced cGVHD ($P < .001$, HR = 1.838) but increased relapse rates (RRs; $P = .028$, HR = 1.198) and decreased OS ($P = .005$, HR = 1.201). In haploidentical transplantation, multivariate analysis showed that ATG/ALG reduced cGVHD ($P < .001$, HR = 1.484) but increased RR ($P < .001$, HR = 1.385).

Conclusions: In allo-SCT for patients with ALL and AML, ATG/ALG contributed to a reduction in grade II-IV aGVHD and cGVHD without affecting TRM and RR in patients who received BM, but was a risk factor for OS affecting TRM and RR in patients who received CB and PB, respectively.

71

Empiric Anti-Thymocyte Globulin (ATG) Dosing in *Ex-Vivo* CD34-Selected Myeloablative Allogeneic Hematopoietic Cell Transplantation (Allo-HCT) May Result in ATG Overexposure That Negatively Affects Outcomes

Michael Scordo [1], *Valkal Bhatt* [2], *Melody Smith* [1], *Katie Thoren* [3], *Patrick Hilden* [4], *Christina Cho* [1], *Gunjan L. Shah* [5], *Molly Maloy* [1], *Esperanza B. Papadopoulos* [1], *Ann A. Jakubowski* [1], *Richard J. O'Reilly* [6], *Hugo Castro-Malaspina* [1], *Roni Tamari* [1], *Brian C. Shaffer* [1], *Miguel-Angel Perales* [1], *Sergio A. Giralt* [1]. [1] *Department of Medicine, Adult Bone Marrow Transplant Service, Memorial Sloan Kettering Cancer Center, New York, NY;* [2] *Department of Pharmacy, Memorial Sloan Kettering Cancer Center, New York, NY;* [3] *Laboratory Medicine, Memorial Sloan Kettering Cancer Center, New York, NY;* [4] *Department of Biostatistics and Epidemiology, Memorial Sloan Kettering Cancer Center, New York, NY;* [5] *Adult Bone Marrow Transplant Service, Memorial Sloan Kettering Cancer Center, New York, NY;* [6] *Department of Pediatrics, Bone Marrow Transplant Service, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Recent studies showed that absolute lymphocyte count (ALC)-based ATG dosing results in optimal exposure after T-cell replete allo-HCT, which translates into lower non-relapse mortality (NRM) and enhanced immune recovery. The effects of ALC-based ATG dosing on outcomes after T-cell depleted allo-HCT are unknown.

Methods: We evaluated adults who underwent *ex-vivo* CD34-selected (CliniMACS CD34 Reagent System) allo-HCT for hematologic malignancies between 2006 and 2012. All