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# **POSTER ABSTRACTS**

## **503.CLONAL HEMATOPOIESIS, AGING AND INFLAMMATION**

### Clonal Hematopoiesis Is Common in Long-Term Survivors of Pediatric Hematopoietic Cell Transplantation, Including Umbilical Cord Blood Transplantation

Konradin F. Müskens, MDMSc,MA<sup>1</sup>, Maaike G.J.M. van Bergen, PhD<sup>2</sup>, Aniek O. de Graaf, PhD<sup>2</sup>, Nienke Wieringa, MD<sup>3</sup>, Brigit M. te Pas<sup>4</sup>, Anne P.J. de Pagter, MDPhD<sup>5</sup>, Joëll E. Bense, MDPhD<sup>5</sup>, Arjan C. Lankester, MDPhD<sup>5</sup>, Leontien C.M. Kremer, MDPhD<sup>3</sup>, Joop H. Jansen, PhD<sup>2</sup>, Geert A. Huls, Prof.<sup>6</sup>, Stefan Nierkens, PhD<sup>3</sup>, Caroline A. Lindemans, MDPhD<sup>3,7</sup>, Mirjam E. Belderbos, MDPhD<sup>3</sup>

<sup>1</sup> Princess Máxima Center for Pediatric Oncology, UTRECHT, Netherlands

<sup>2</sup>Department of Laboratory Medicine, Laboratory of Hematology, Radboud University Medical Center, Nijmegen, Netherlands

<sup>3</sup>Princess Máxima Center for Pediatric Oncology, Utrecht, Netherlands

<sup>4</sup> Princess Maxima Centre for Pediatric Oncology, Utrecht, Netherlands

<sup>5</sup> Division of Stem cell Transplantation, Department of Pediatrics, Willem-Alexander Children's Hospital, Leiden University Medical Center, Leiden, Netherlands

<sup>6</sup>Department of Hematology, University Medical Center Groningen, Groningen, Netherlands

<sup>7</sup>Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, Netherlands

### Background

1. Approximately 20.000 to 200.000 hematopoietic stem and progenitor cells (HSPCs) contribute to steady-state adult hematopoiesis. During ageing, the overall diversity of the HSPC pool decreases, which is in part driven by the selective expansion of HSPC clones with driver mutations, a process called clonal hematopoiesis (CH). CH is an age-related condition that predisposes to hematologic malignancy, cardiovascular disease, and all-cause mortality. Hematopoietic stem cell transplantation (HCT) recipients are at increased risk of CH, but the mechanisms driving the emergence and expansion of CH clones are largely unknown. Furthermore, the prevalence of CH in pediatric HCT recipients, in whom the long-term consequences of CH are particularly relevant, remains to be defined.

Aim

To determine the prevalence and risk factors of CH in long-term survivors of HCT at pediatric age. *Methods* 

We included survivors of HCT at pediatric age, with a minimum survival of 5 years after HCT. CH was assessed by targeted, error-corrected sequencing of mutations in 27 cancer driver genes in whole blood, at a variant allele frequency detection threshold of 1%. HSC age was calculated by the sum of the age of the donor and the interval after HCT. In case the age of a donor was unknown (n=53), the median age for donors of the same donor relation were used (i.e., 12.6 years for sibling donors and 28.7 for matched unrelated donors). Clinical characteristics were compared using the Wilcoxon signed ranked test for continuous variables and Chi-squared or Fisher's exact test for categorical variables. *Results* 

Here, we report the interim results of the first 120 HCT survivors in this study. The median age of the survivors was 20.4 years (range 6.7-51.8), and the median interval after HCT was 11.8 years (range 5.2-38.2). Indications for HCT were hematooncology (n=95), bone marrow failure (n=22), or immune deficiency (n=3). The median calculated age of the HSCs was 31 years (range 5.2-61.8). CH was present in 13.3% of survivors (n=16). Mutated genes were *DNMT3A* (n=15), *TET2* (n=4) and *MPL* (n=1), with three individuals having more than one driver mutation. The median variant allele frequency of the CH clones was 2.2%, but allele frequencies up to 30% were found. No differences were observed in recipient age or interval after HCT between individuals with or without CH (Figure 1A). However, the age of the HSCs was significantly higher in individuals with CH compared to those without (38.6 versus 26.3 years, p = 0.01, Figure 1B). Surprisingly, we detected CH in two recipients of umbilical cord blood grafts, at an interval of 11 and 15 years after HCT. *Conclusion* 

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Clonal hematopoiesis is common in long-term survivors of pediatric HCT. After HCT, the prevalence of CH is related to the age of the transplanted HSCs, rather than the age of the survivor. The presence of CH in cord blood HSCs within two decades after HCT suggests that HCT-related factors may drive the *de novo* emergence and/or outgrowth of donor-derived CH. Ongoing research is aimed at investigating how factors such as stem cell source and post-transplant complications affect clonal expansion after HCT. Furthermore, we are investigating the prevalence of CH in an age-matched control cohort using the same detection pipeline, enabling direct comparison of the prevalence of CH in HCT survivors compared to the general population.

**Disclosures Nierkens:** Sobi: Membership on an entity's Board of Directors or advisory committees. **Lindemans:** ExCellThera: Other: Data and safety monitoring board; Orchard Therapeutics: Membership on an entity's Board of Directors or advisory committees; Sobi: Membership on an entity's Board of Directors or advisory committees; Pfizer: Patents & Royalties: IL-22 in GvHD.



Figure 1. Stem cell age is higher in long-term survivors of pediatric HCT with clonal hematopoiesis. A-B) Boxplots showing the survivor age (A) and calculated age of the transplanted donor HSC (B) in survivors with CH (red) and without CH (grey). Dots represent individual survivors, with blue dots indicating that donor age was estimated (see Methods). Abbreviations: HSC: hematopoietic stem cell; CH: clonal hematopoiesis

Figure 1

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