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POSTER ABSTRACTS

503.CLONAL HEMATOPOIESIS, AGING AND INFLAMMATION

Exploring Clonal Hematopoiesis in Chronic Graft Versus Host Disease Patients: A Comprehensive Study

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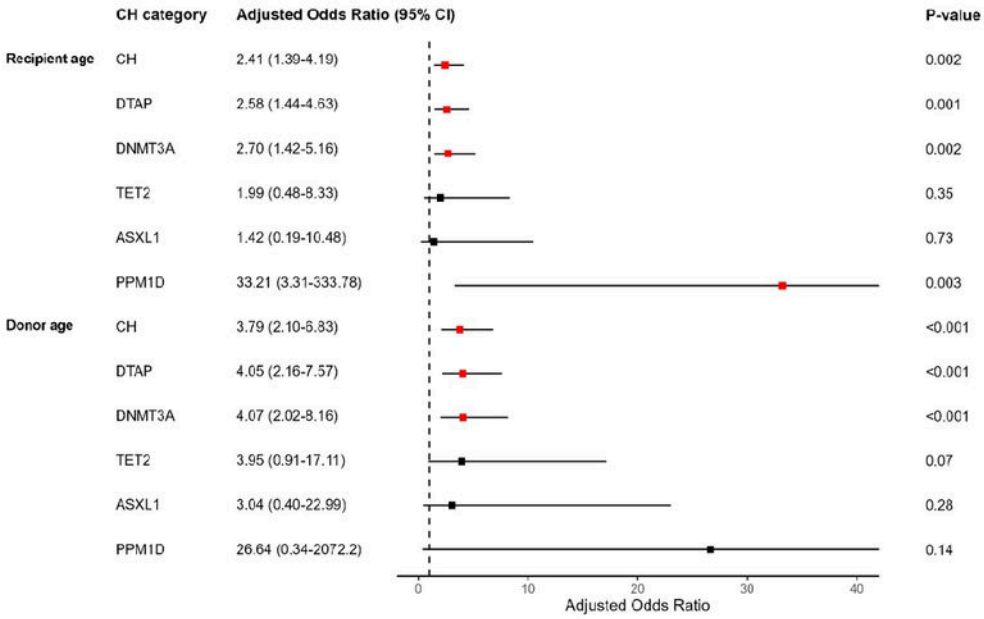
Introduction
Clonal hematopoiesis (CH) is a prevalent condition characterized by the presence of genetic mutations in hematopoietic cells, without being associated with any overt hematological malignancy. Emerging evidence has linked CH to various health complications, potentially contributing to higher morbidity rates in cancer survivors and individuals with chronic inflammatory diseases. Increased inflammation has been identified as a consequence of CH-related mutations, which may underlie these risks. Chronic graft versus host disease (cGVHD), debilitating complication of allogeneic hematopoietic stem cell transplantation (allo-HSCT), is a multisystem inflammatory disease. However, to date, the relationship between CH and cGVHD remains poorly understood. This study aims to investigates the potential role of CH in increasing the risk of developing cGVHD.
Methods
Research was conducted on patients who met the following inclusion criteria; (1) adult (age ≥ 18 years) acute myeloid leukemia (AML) patients who had previously consented to blood banking at a human resources bank and signed a residual specimen research agreement (IRB: H-2202-100-1302); (2) received allo-HSCT between Jul 2013 and Oct 2020; (3) experienced cGVHD of any NIH severity; (4) had peripheral blood sample taken after the occurrence of cGVHD but without relapse at that time, evidenced by >95% donor chimerism. The sequencing of 24 CH-related genes reported to date was performed at a sequence depth of ≥1000X, and the results were reported with a sensitivity of 99.9% and an accuracy of 99.9%. Analysis was conducted on patients with Variant Allele Frequency (VAF) ranging from 2.0% to less than 30.0%, classifying them as CH positive.
Result
A total of 134 patients who met the inclusion criteria were included in the analysis. The mean age at matched sibling donors (MSD) (n=41, 30.6%), unrelated donors (UD) (n=38, 28.4%) and haplo-identical donors (HID) transplants (n=55, 41.0%) was 48, 45 and 43 years for recipients, respectively, with no statistically significant difference (p=0.220). However, there was a significant difference in the mean age of donors, with 45, 32 and 32 years for MSD, UD and HID transplants, respectively (p<0.001).
Among the cGVHD patients, 11.9% (16/134) tested positive for CH. The majority of these CH+ patients had a DNMT3A mutation (11) followed by TET2 (2), ASXL1 (1) and PPM1D (1). Between the CH- and CH+ groups, there were no statistically significant differences in age (both recipient and donor), gender, and clinical outcomes including relapse and death. A trend towards a higher incidence of CH+ was observed in patients receiving HID transplants, with 3/41 (7.3%) for MSD, 3/38 (7.9%) for UD, and 10/55 (18.2%) for HID, although this difference was not statistically significant (p=0.177). In addition, we could not observe the differential impact of donor age on the incidence of CH+ after allo-HSCT. The distribution of CH was further analyzed based on clinical outcomes, dividing patients into severe cGVHD and non-severe cGVHD groups. The results showed

that patients with a mutation in the TET2 gene, which contributes to CH, accounted for 6.9% (2/29) of the total patients in the severe cGVHD group, while it was 0% (0/105) in the non-severe cGVHD group.
Next, we compared CH data from cGVHD patients to a cohort of 5205 healthy individuals in Korea, where a CH positivity rate of 7.9% was observed. We found a statistically significant increase in the odds ratio for CH positivity in the overall cGVHD population after adjusting for age. The highest detection of CH, including the DNMT3A gene, was observed when adjusting for recipient age (odds ratio of CH 2.41[1.39-4.19], p= 0.002) and when adjusting for donor age (odds ratio of CH 3.79[2.10-6.83], p= 0.001).
Conclusion
In this study, we found that 11.9% of cGVHD AML patients who underwent allo-HSCT tested positive for CH, with DNMT3A mutation being the most common. There was a trend towards a higher incidence of CH+ in HID transplant although it was not statistically significant. Compared to healthy individuals, cGVHD patients had a significant higher risk for CH positivity, particularly when adjusting for age. For the deeper understanding of CH's role in post-transplant complications, further analysis with incorporating the data regarding baseline genetic information from recipients and donors and non-cGVHD patients after allo-HSCT would be warranted.

Disclosures An: *Genome Opinion:* Current Employment, Current holder of *stock options* in a privately-held company. **Lim:** *Genome Opinion:* Current Employment. **Koh:** *BMS Korea:* Consultancy; *Takeda Korea:* Consultancy; *Janssen Korea:* Consultancy; *Novartis Korea:* Consultancy; *Deep Metrics:* Current equity holder in private company; *Curocell:* Current equity holder in private company; *Proteina:* Current holder of *stock options* in a privately-held company; *Tomocube:* Current holder of *stock options* in a privately-held company, Membership on an entity's Board of Directors or advisory committees; *Sanofi Genzyme:* Research Funding; *Genome Opinion:* Current Employment, Current equity holder in private company, Membership on an entity's Board of Directors or advisory committees. **Kim:** *AML-Hub:* Consultancy, Other; *BMS&Celgene:* Consultancy, Honoraria, Other: Participation on a Data Safety Monitoring Board or Advisory Board; *Daiichi Sankyo:* Consultancy; *Abbvie:* Consultancy, Honoraria, Other: Participation on a Data Safety Monitoring Board or Advisory Board; *VigenCell:* Consultancy; *Meiji Pharm Co.:* Consultancy; *Sanofi Genzyme:* Consultancy; *Ingenium:* Consultancy; *Novartis:* Consultancy, Other: Participation on a Data Safety Monitoring Board or Advisory Board; *Handok:* Consultancy, Honoraria, Other: Participation on a Data Safety Monitoring Board or Advisory Board; *Pfizer:* Consultancy; *BL & H:* Other: Grant; *SL VaxiGen:* Consultancy; *Amgen:* Consultancy; *Takeda:* Consultancy; *AIMS Bioscience:* Consultancy; *LG Chem:* Consultancy; *Astellas:* Consultancy, Honoraria; *Boryung Pharm Co.:* Consultancy; *Janssen:* Consultancy.

VAF≥2.0%	CH negative (N=118)	CH positive (N=16)	P value
Sex (M)	70 (59.3%)	7 (43.8%)	0.361
Age(recipient)	44.7 ± 13.0	49.9 ± 9.7	0.124
Age(donor)	35.7 ± 13.3	37.9 ± 14.8	0.533
Donor type			0.177
- Matched sibling	38 (32.2%)	3 (18.8%)	
- Familial mismatched	45 (38.1%)	10 (62.5%)	
- Unrelated	35 (29.7%)	3 (18.8%)	
Relapse	20 (16.9%)	3 (18.8%)	1.000
Death	21 (17.8%)	5 (31.2%)	0.347
Severe cGVHD	25 (21.2%)	4 (25.0%)	0.749
- GI cGVHD	11 (9.3%)	1 (6.7%)	1.000
- Liver cGHVD	39 (33.1%)	4 (26.7%)	0.838
- Lung cGHVD	23 (19.5%)	4 (26.7%)	0.757

<Table 1. Clinical Differences in cGVHD Patients According to the Presence of Clonal Hematopoiesis >



< Figure 1. Forest plot of adjusted odds ratio clonal hematopoiesis and cGVHD >

Figure 1

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