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Impact of donor clonal hematopoiesis in older matched-related transplantation

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Acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) are myeloid malignancies affecting older patients, who have historically often been considered ineligible for allogeneic stem cell transplantation (allo-SCT) due to their age and pre-existing comorbidities. However, reduced intensity conditioning (RIC) regimens have allowed more older patients to receive allo-SCT, often from older sibling donors.

The presence of preleukemic mutations in peripheral blood (PB) samples is termed clonal hematopoiesis of indeterminate potential (CHIP). CHIP is defined as the absence of definitive morphologic evidence of hematologic neoplasms, with the presence of a somatic mutation with a variate allele frequency (VAF) of > 2%. The incidence of CHIP increases with age and comes with an increased risk of developing myeloid malignancies and cardiovascular complications. Therefore, using older donors with CHIP may impact the outcomes of patients undergoing transplantation.

During the 61st meeting of the American Society of Hematology (ASH), Betul Oran, MD Anderson Cancer Center, Houston, US, presented the results from a study which evaluated the impact of donor clonal hematopoiesis on the risk of acute graft-*versus*-host disease (GvHD, aGvHD) and patient outcomes. The trial was conducted in patients with AML or MDS who received a transplant from a matched-related donor (MRD) aged 55 years or older.

Study design and patient characteristics

- Retrospective analysis of 421 patients with AML/MDS who underwent allo-SCT from an older donor (≥ 55), between 2000 and 2018 at MD Anderson Cancer Center
    - DNA samples were available from 363 healthy older donors at the time of donation
- Using donor PB samples taken at the time of donation, targeted deep sequencing of 300 genes was conducted
- CHIP was identified using modified Mutect and Pindel algorithm
    - Variants with a VAF < 2% were excluded
- Patient/donor characteristics (given as CHIP positive *vs* negative):
    - Median donor age: 63 (range: 53–78) *vs* 60 (55–70) (p= 0.004)
    - Follow-up for survivors: 63 *vs* 64 months (p= not reported)
    - Diagnosis of AML *vs* MDS: 58% *vs* 53% (p= 0.5)
    - RIC *vs* myeloablative conditioning: 48% *vs* 50% (p= 0.8)
    - PB stem cells *vs* bone marrow: 84% *vs* 89% (p= 0.3)

- Tacrolimus-based GvHD prophylaxis *vs* post-transplant cyclophosphamide: 82% *vs* 89% (p= 0.1)

CHIP distribution

- Of the 363 donors, 20% (n= 71) had CHIP
  - Most commonly with only one mutation (89%)
  - The median VAF was 0.0685
- Most frequently mutated genes:
  - *DNMT3A*: 45% (32/71)
  - *TET2*: 25% (18/71)
  - *PPM1D*: 11% (8/71)
  - *ASXL1*: 10% (7/71)
- CHIP prevalence increased with donor age, p=0.004
  - Median donor age, years (range):
    - CHIP positive (n=71): 63 (53–78)
    - CHIP negative (n=292): 60 (55–70)

Impact of CHIP on engraftment

- There were no statistically significant differences in engraftment and recovery rates
- The values given below are for CHIP positive (n=57) *vs* CHIP negative (n=245) donors:
  - Engraftment: 98% *vs* 97%
  - Median time to neutrophil recovery: 12 (7–27) *vs* 12 (5–30) days, p= 0.3
  - Median time to platelet recovery: 14 (9–67) *vs* 13 (4–71) days, p= 0.6

Impact of CHIP on clinical outcome

- Clinical outcome analysis was restricted to 302 patients who received:
  - First allo-SCT from MRD
  - PB as stem cell source
- In this cohort, GvHD prophylaxis was tacrolimus/methotrexate in 90% of cases
- There were no significant associations between donor CHIP and treatment-related mortality (TRM), overall survival (OS) or progression-free survival (PFS) as shown in **Table 1**

Table 1. Impact of CHIP on transplant outcomes

	CHIP positive	CHIP negative	HR	95% CI	p value
N	57	245	-	-	-
Relapse incidence (RI) at 5-years	Not reported (NR)	NR	0.9	0.5–1.5	0.7
Age-adjusted RI at 5-years	NR	NR	0.9	0.6–1.4	0.7
Progression incidence at 5-years, %	40	44	0.9	0.5–1.4	0.5
TRM at 6 months, %	12	9	1.6	0.5–4.9	0.4
Age adjusted RM at 6 months	NR	NR	1.3	0.6–2.9	0.5
PFS at 5-years, %	38	36	0.97	0.7–1.4	0.9
Age adjusted PFS at 5-years	NR	NR	0.96	0.7–1.4	0.8
OS at 5-years, %	43	41	1.05	0.7–1.5	0.8

Impact of CHIP on rate of GvHD

- There was an increased incidence in aGvHD both grade II-IV and III-IV with donor CHIP as shown in **Table 2**
- However, the same increase was not seen for chronic GvHD (cGvHD)
- The investigators also analyzed the impact of CHIP on aGvHD by donor age (**Table 2**)

Table 2. Impact of donor CHIP on rates of GvHD

	CHIP positive	CHIP negative	HR	95% CI	p value
N	57	245	-	-	-
Grade II-IV aGvHD at 6 months					

Total, %	51	27	2.1	1.4–3.3	**0.001**
Donor > 65 years, %	54	27	2.1	1.05–4.4	**0.04**
Donor ≤ 65 years %	48	28	2	1.1–3.5	**0.001**
Grade III-IV aGvHD at 6 months					
Total, %	16	5	3.2	1.3–7.4	**0.008**
Donor > 65 years, %	17	7	2.4	0.6–9.5	0.2
Donor ≤ 65 years %	15	5	3.5	1.1–10	**0.03**
cGvHD at 5 years, %	23	35	0.65	0.4–1.2	0.2

Conclusion

In patients with AML or MDS receiving allo-SCT with PB stem cells from an older MRD as the source, donor CHIP was associated with a significant increase in grade II-IV and III-IV aGvHD. However, engraftment, risk of progression and OS were unaffected. Further studies are warranted in order to better understand the molecular mechanisms of aGvHD and to identify therapeutic interventions to improve CHIP donor-induced aGvHD.

References

1. Oran B. *et al.,* Donor Clonal Hematopoiesis Increases Risk of Acute Graft Versus Host Disease after Matched Related Transplantation in AML and MDS Patients. 61st meeting of the American Society of Hematology (ASH), Orlando, US. 2019 Dec 07. Oral abstract #47