Long-Term Monitoring of Plasma Cell-Free DNA Chimerism in 100 Acute Leukemia Patients Following Allo-HSCT: A Prospective Cohort Study

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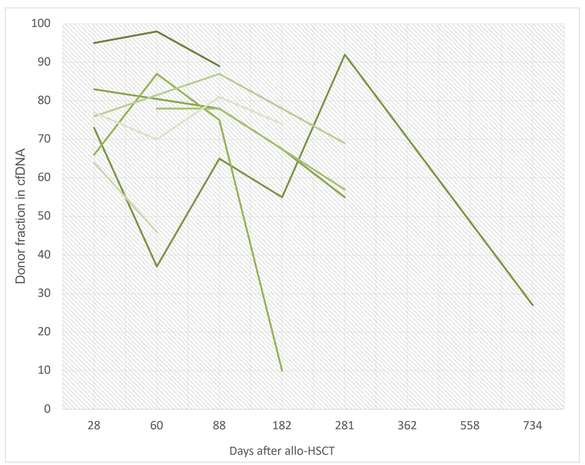
Background

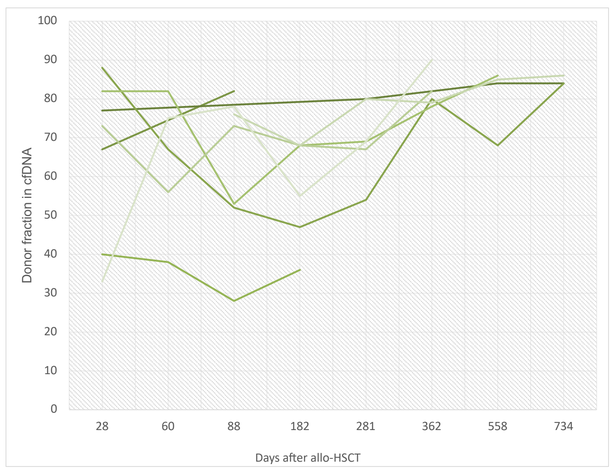
After allogeneic hematopoietic stem cell transplantation (allo-HSCT), increased recipient cell-free DNA (cfDNA) may indicate recipient hematopoiesis, relapse, or cell death, serving as an early marker of chimerism instability.

Methods

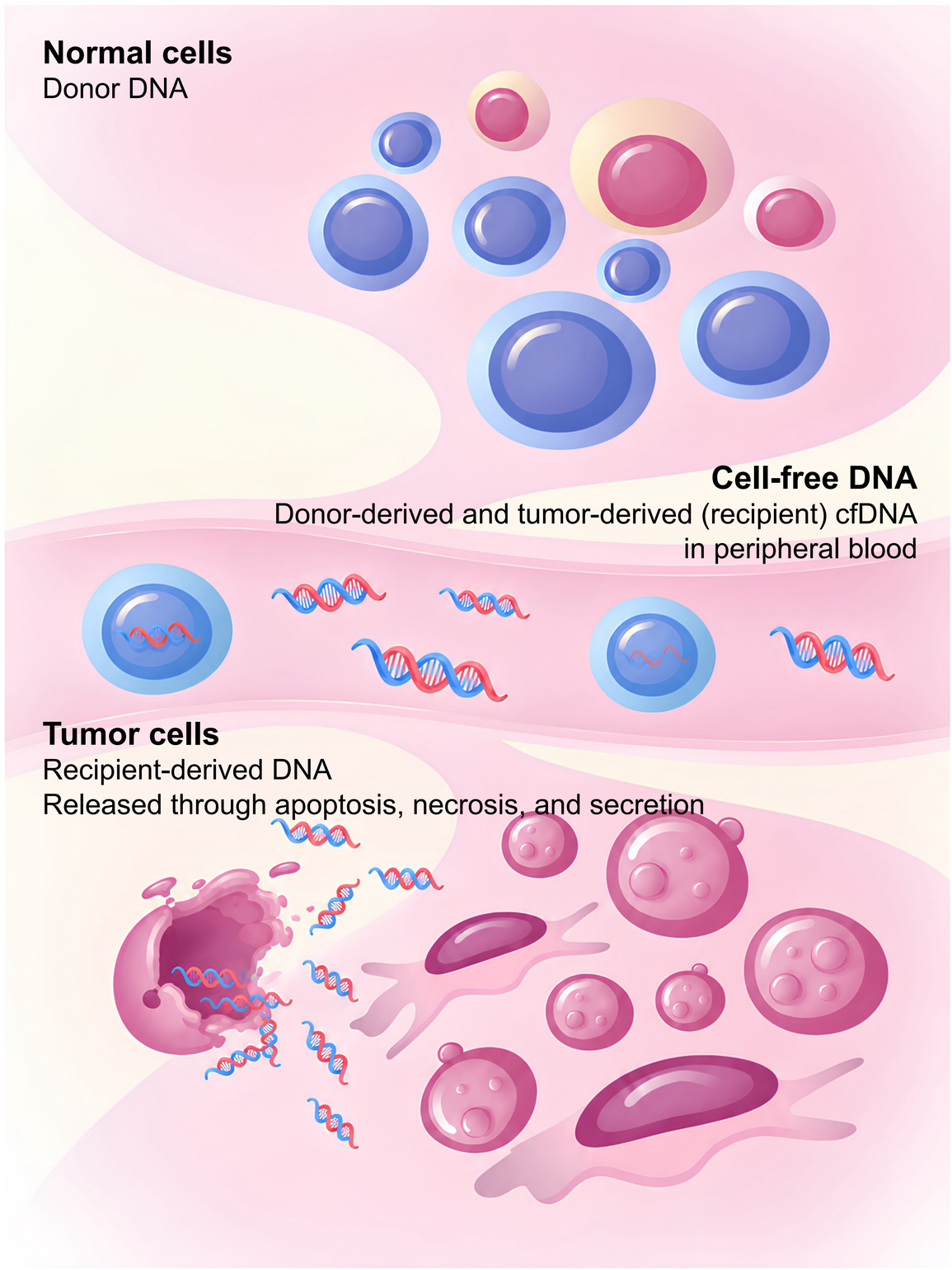
DNA was isolated from peripheral blood (PB), bone marrow (BM), and plasma of 100 acute leukemia patients (61 AML, 39 ALL) who underwent allo-HSCT (Aug 14, 2023 - Feb 25, 2025). Chimerism was monitored on days 30, 60, 90, 180, 270, 360, 540, and 720 post-transplant. A control group of 12 patients in long-term remission (>3 years) was assessed once. BM and PB samples were collected simultaneously. STR-PCR analysis used the CORDIS Plus kit (Gordiz, Russia) and GeneMapper v4.0 (Applied Biosystems, USA).



Dynamics of the donor DNA fraction in circulating cell-free DNA in plasma from patients with relapse; cases showing a decrease in the donor DNA fraction, presumably associated with relapse development, are presented (n=8).



Dynamics of the donor DNA fraction in circulating cell-free DNA in plasma from patients with relapse; cases showing an increase or stable donor DNA fraction, not associated with relapse development, are presented (n=8).



Adapted from S. Yu. Smirnov et al., "Cell-free DNA in the plasma of patients with diffuse large B-cell lymphoma and high-grade B-cell lymphoma ("double-hit"/"triple-hit")."

Results

Controls with complete donor chimerism in PB/BM showed a median donor fraction of 87% (range, 76%–95%) in plasma cfDNA. In the study cohort, 43 patients completed follow-up, while 30 withdrew early due to relapse-related death, infections, or second allo-HSCT; 25 patients were followed for ≥540 days, and 2 for 360 days. In relapsing patients, plasma donor cfDNA declined 1–2 time points before BM chimerism decreased, confirming its potential as an early indicator of instability. However, cfDNA chimerism showed high biological variability: some patients maintained high donor cfDNA despite relapse, while others showed decreased levels during stable remission. Thus, plasma cfDNA reflects total cell turnover, is nonspecific, and cannot guide therapy alone.

Conclusion

This prospective study shows that the plasma donor DNA proportion is a nonspecific marker of cell death rather than an independent diagnostic test.

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