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Post-transplant outcomes of patients with therapy-related AML following treatment for prior lymphoid malignancy

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Secondary acute myeloid leukemia (sAML) comprises a heterogenous group of diseases. It is most often derived from conditions such as myelodysplastic syndrome (MDS) and myeloproliferative neoplasms (MPNs), though there is a significant population with therapy-related AML (t-AML) related to prior treatment for a hematological lymphoid malignancy. Patients with t-AML typically have poor outcomes due to the pretreatment received, and/or an older age at diagnosis. Allogeneic hematopoietic stem cell transplant (allo-HSCT) is potentially curative for these patients, though relapse remains an issue. The allo-HSCT outcomes of patients who developed a t-AML after treatment of a B-cell malignancy have not been well studied, and the potential impact of choice of conditioning regimens on post-transplant outcomes has not been discerned.

Katie S. Gatwood, Vanderbilt University Medical Center, Nashville, US, and colleagues conducted a multicenter, retrospective study using the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT) registry. They aimed to evaluate the impact of myeloablative (MAC) *versus* reduced intensity conditioning (RIC) regimen on allo-HSCT outcomes in patients with t-AML following a lymphoid malignancy.

Patient characteristics

The authors analyzed data of adult patients with sAML (n= 549) who had previously been treated for a lymphoid malignancy and had received their first allo-HSCT between 2000–2016. The prior malignancies included acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), lymphoma and plasma cell dyscrasias. Patient characteristics at baseline are shown in **Table 1.**

Table 1. Baseline characteristics by conditioning regimen

Conditioning regimen	Myeloablative (MAC)	Reduced intensity (RIC)
N	258 (47%)	291 (53%)
Median age at transplant (years)	47.8	55.9
Median time from diagnosis to transplant (months)	4.7	4.7

Previous diagnosis:		
· ALL	· 25 (9.7%)	· 15 (5.2%)
· CLL	· 29 (11.2%)	· 36 (12.4%)
· Lymphoma	· 194 (75.2%)	· 219 (75.3%)
· Multiple myeloma (MM)	· 10 (3.9%)	· 21 (7.2%)
AML cytogenetics		
· Favorable	· 8 (3.1%)	· 9 (3.1%)
· Intermediate	· 73 (28.3%)	· 96 (33%)
· Adverse	· 73 (28.3%)	· 68 (23.4%)
· Missing	· 104 (40.3%)	· 118 (40.6%)
Disease status at allo-HSCT		
· Active	· 80 (31%)	· 92 (31.6%)
· Complete remission (CR) 1	· 161 (62.4%)	· 181 (62.2%)
· CR2	· 17 (6.6%)	· 18 (6.2%)

Donor type		
· Matched sibling (MSD)	· 93 (36%)	· 90 (30.9%)
· Unrelated (URD)	· 126 (48.8%)	· 174 (59.8%)
· Haploidentical	· 25 (9.7%)	· 15 (5.2%)
· Cord blood transplant	· 14 (5.4%)	· 12 (4.1%)

Efficacy

The efficacy results are shown in **Table 2**, by total cohort, and by conditioning regimen. Patients receiving RIC had a lower risk of non-relapse mortality (NRM), improved leukemia-free survival (LFS), and superior overall survival (OS, **Table 3**) in multivariate analysis. The choice of conditioning regimen did not significantly impact relapse incidence though.

Table 2. Efficacy results for the total cohort and by conditioning regimen and multivariate analysis

	Total cohort, % **95% CI**	**MAC, %** **95% CI**	**RIC, %** **95% CI**	***p* value**
Two-year LFS	31.7 27.5–35.9	27.9 22–33.8	35.1 29.2–41	0.055
Two-year RI	39.1 34.8–43.4	38.6 32.3–44.9	39.6 33.7–45.5	0.82
Two-year OS	37.4 33–41.8	34.2 27.9–40.5	40.2 34.1–46.3	0.074

Two-year NRM	28.9 25–33	33.3 27.4–39.4	25.3 20.2–30.6	0.04
Two-year graft-*versus*-host disease (GvHD)-free relapse-free survival (GRFS)	22.8 19–26.6	19.8 14.5–25.1	25.5 20.1–30.9	0.148

Table 3. Factors *significantly* associated with outcomes in multivariate analysis

	HR	**95% CI**	***p* value**
LFS			
Conditioning regimen (MAC vs RIC)	0.67	0.52–0.85	0.001
Prior autologous HSCT (yes)	1.3	1.01–1.67	0.04
Cytogenetics (adverse vs favorable)	3.15	1.35–7.37	0.008
Active disease at transplant vs CR1	1.68	1.31–2.56	< 0.001
CBT vs MSD	0.9	0.51–1.61	0.04
Donor (female to male)	1.35	1.03–1.77	0.028
OS			
Conditioning regimen (MAC vs RIC)	0.69	0.53–0.89	0.004
Cytogenetics (intermediate vs favorable)	3.56	1.01–11.76	0.037

Cytogenetics (adverse vs favorable)	6.61	2–21.85	0.002
Active disease at transplant vs CR1	1.57	1.2–2.04	0.001
RI			
Active disease at transplant vs CR1	2.25	1.62–3.13	< 0.001
Karnofsky performance status (KPS, < 80% vs ≥ 80%)	0.46	0.29–0.72	0.001
NRM			
Conditioning (MAC vs RIC)	0.58	0.4–0.83	0.003
Cytogenetics (adverse vs favorable)	4.64	1.05–20.54	0.043
KPS (< 80% vs ≥ 80%)	0.4	0.24–0.66	< 0.001
Donor (female to male)	1.521	1.02–2.27	0.04
GFRS			
Conditioning regimen (MAC vs RIC)	0.79	0.62–0.99	0.045
Cytogenetics (adverse vs favorable)	2.82	1.29–6.19	0.02
Active disease at transplant vs CR1	1.66	1.3–2.13	< 0.001
KPS (< 80% vs ≥ 80%)	0.47	0.34–0.66	< 0.001
Donor (female to male)	1.32	1.02–1.71	0.037

Rates of GvHD are shown in **Table 4**. Unrelated donor transplant was associated with higher rate of grade II–IV aGvHD (HR: 1.67, 1.06–2.63, *p*= 0.027) and a KPS of > 80% was associated with lower rate of grade III–IV aGvHD (HR: 0.45, 0.2–1, *p*= 0.049).

Table 4. Cumulative incidence of GvHD for total cohort and by conditioning regimen

	Total cohort, % **95% CI**	**MAC, %** **95% CI**	**RIC, %** **95% CI**	***p* value**
Grade II–IV acute GvHD (aGvHD) at day 100 post-transplant	30.6 26.6–34.6	32.7 26.9–38.7	28.6 23.3–34.1	0.2
Grade III–IV aGvHD at day 100 post-transplant	13.7 10.9–16.8	15.37 11.1–20.1	12.3 8.7–16.5	0.26
Chronic GvHD (cGvHD) at two-years	27 23–31.1	23.7 18.3–29.6	30.1 24–36.4	0.16
Extensive cGvHD at two-years	12.8 9.9–16	11.4 7.5–16.1	14 10–18.6	0.38

Other variables associated with poor outcomes in the total cohort were; older age, adverse cytogenetics and active disease at time of transplant.

Deaths

In total, 171 patients receiving MAC and 174 patients receiving RIC died. The main causes (>10% of patients) were:

Given as MAC vs RIC

- Relapse: 40.8% *vs* 45.9%
- Infection: 22.6% *vs* 19.8%
- GvHD: 20.1% *vs* 16.9%

Conclusion

This study has some limitations, including the retrospective nature, potential for selection bias regarding intensity of conditioning, a lack of molecular characterization of AML subtype, a lack of analysis by disease risk, and missing cytogenetic data in around 40% of patients.

In summary, this analysis supports the use of allo-HSCT with RIC for patients with sAML following a prior lymphoid malignancy since patients treated with RIC regimens had a lower risk of NRM and improved LFS, OS and GFRS.

References

1. Gatwood K.S. *et al.*, Transplant outcomes for patients with therapy-related acute myeloid leukemia with prior lymphoid malignancy: an ALWP of EBMT study. Bone Marrow Trans. 2019 Sep 16. DOI: 10.1038/s41409-019-0673-3