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The late effects of allogenic hematopoietic cell therapy in adolescent and young adults with acute myeloid leukemia

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Allogenic hematopoietic stem cell transplantation (allo-HSCT) is frequently used as a curative treatment in adolescents and young adults (AYAs) with acute myeloid leukemia (AML), with more than 50% of patients experiencing long-term survival.[1] However, there have been few studies on the late effects of allo-HSCT in AYAs that could help to support these patients and their age-related physiological and/or psychosocial challenges.

Catherine J. Lee, Huntsman Cancer Institute, University of Utah, US, and colleagues conducted a retrospective study to investigate the late effects, survival, and mortality up to 10 years after allo-HSCT treatment in AYAs with AML. They also compared the late effects based upon the type of myeloablative conditioning (MAC) used prior to HSCT: total body irradiation (TBI) or high-dose chemotherapy only. The results were published earlier last month in the journal *Blood Advances*.[2]

Methods[2]

The analysis included 826 AYA patients (aged 15–39 years) with AML who had undergone allo-HSCT between 2000 and 2014; who had survived at least one-year disease-free after allo-HSCT; and had been reported to the Center for International Blood and Marrow Transplant Research (CIBMTR).

- Late effects were reported using CIBMTR comprehensive report forms
- Participants were selected by weighted randomization
- Overall survival (OS) was defined as the time from HSCT until death as a result of any cause
- Leukemia-free survival (LFS) was defined as the time until disease relapse or death
- Non-relapse mortality (NRM) was defined as death in the absence of disease relapse or progression from the time of HSCT

Key results[2]

Patient characteristics

- Of the 826 AYA patients with AML, 390 (47%) had received TBI and 436 (53%) received chemotherapy-only MAC
- The median follow-up of the population was 77 months (range, 12–194) and was longer in the TBI group (94 months) compared to the chemotherapy-only group (73 months)
- acute GVHD (aGVHD) was seen in 36% of the patients overall, with Grades 3–4 aGVHD reported in 9% of patients, both in the TBI and non-TBI-based conditioning group

- Grades 2–4 chronic graft-*versus*-host disease (cGVHD) occurred in 55% of the total study cohort, with extensive cGvHD in 45% and 44% of the TBI and non-TBI group, respectively
- 177 deaths (21%) were documented, mostly due to disease recurrence

Subsequent neoplasms

- The estimated 10-year cumulative incidence of subsequent neoplasms (SNs) was 4% (95% confidence interval [CI], 2–6%) and was not significantly different between the TBI group and chemotherapy-only group (p = 0.73)

Non-malignant late effects

- Of the total study cohort, 22% of patients reported at least one non-malignant late effect, with a greater frequency (22% *vs* 12%) reported in patients that had undergone TBI compared with chemotherapy-only MAC
- The 10-year cumulative incidence of non-malignant late effects in the total study cohort included
  - gonadal dysfunction 10% (95% CI, 8–13%)
  - cataracts 10% (95% CI, 7–13%)
  - avascular necrosis 8% (95% CI, 5–10%)
  - diabetes mellitus 5% (95% CI, 3–7%)
  - hypothyroidism 3% (95% CI, 2–5%)
- A breakdown of the malignant and non-malignant late effects can be seen in **Table 1**

Table 1. Estimated cumulative incidence of late effects for AYA patients with AML after allo-HSCT[2]

	All patients (N = 826)		**TBI (n = 390)**		**Chemotherapy only (n = 436)**		
Late effect	**No.**	**95% CI**	**No.**	**95% CI**	**No.**	**95% CI**	***p value**
SNs							0.73
2y	0	0–1	0	0–1	0	0–1	
5y	1	0–2	1	0–2	1	0–2	
10y	4	2–6	3	1–7	4	1–8	

Avascular necrosis							0.2
2y	2	1–4	3	2–5	2	1–3	
5y	5	4–7	7	4–9	4	3–7	
10y	8	5–10	9	6–13	6	4–9	
Cataracts							**< 0.001**
2y	1	0–1	1	0–3	0	0–1	
5y	5	3–7	8	6–12	1	0–2	
10y	10	7–13	15	11–19	5	2–10	
Diabetes mellitus							0.21
2y	1	1–2	3	1–5	0	0–1	
5y	3	2–4	4	2–6	2	1–4	
10y	5	3–7	5	3–9	4	1–8	
Hypothyroidism							0.38
2y	1	0–1	1	0–2	0	0–1	
5y	2	1–3	2	1–4	2	1–3	

10y	3	2–5	4	2–7	3	1–5	
Gonadal dysfunction							0.98
2y	4	2–5	4	2–6	3	2–5	
5y	7	5–9	7	5–10	6	4–9	
10y	10	8–13	10	6–13	11	7–16	

*p value for comparison of TBI and chemotherapy-only MAC regimes.

- TBI-based MAC was independently associated with a higher risk of cataracts only (hazard ratio [HR] 4.98; 95% CI, 2.42–10.24; p < 0.0001)
- Development of cGVHD was independently associated with an increased risk of
  - cataracts (HR 3.22; 95% CI, 1.65–6.29; p = 0.0006)
  - avascular necrosis (HR 2.49; 95% CI, 1.29–4.76; p = 0.006)
  - diabetes mellitus (HR 3.36; 95% CI, 1.12–10.04; p = 0.03)

Survival outcomes

- NRM at 10 years in the total population was 14% (95% CI, 11–17%) and did not differ based on MAC type
- The cumulative incidence of relapse at 10 years was significantly lower in patients that had received TBI compared with chemotherapy alone (13% *vs* 19%; p = 0.01), although this was not reflected by differences in LFS or OS
- Increased mortality was associated with the presence of cGVHD at one year after HSCT (HR 1.62; 95% CI, 1.19–2.21; p < 0.002) and the development of SNs (HR 7.97; 95% CI, 3.62–17.53; p < 0.0001)
- Estimated 10-year OS and LFS were 73% and 70%, respectively, and did not differ based on MAC type

Conclusion[2]

This study demonstrates that late effects among AYA long-term survivors of allo-HSCT are frequent, with nearly a quarter of patients developing more than one late effect. Although the prevalence of one or more late effects were greater in those who received TBI MAC, the estimated cumulative incidences of late effects and SNs were not significantly associated with the type of MAC. The exception to this was the development of cataracts, which were more likely to develop after high-dose TBI.

Limitations of the study include a relatively short follow-up time of survivors after HSCT, therefore, conditions that are known to occur even decades after HSCT, such as cardiac events[3] and SNs, would not have been captured in this cohort.

As late effects were more closely linked to cGVHD than the type of conditioning, the authors highlight the importance of developing allo-HSCT procedures and related treatments that result in less cGVHD and suggest that more comprehensive, long-term follow-ups are required in AYAs with AML.

The authors recommend systematic assessment of late effects in AYAs, which would help in developing AYA-focused survivorship guidelines and care plans, similar to those done for survivors of childhood cancers.

References

1. Majhail NS, Tao L, Bredeson C, et al. Prevalence of hematopoietic cell transplant survivors in the United States. *Biol Blood Marrow Tr*. 2013;19(10):1498-501. DOI: 10.1016/j.bbmt.2013.07.020

2. Lee C.J, Kim S, Tecca H.R, Bo-Subait S, Phelan R, Brazauskas R, Buchbinder D, Hamilton B.K, Battiwalla M, Majhail NS, Lazarus HM, et al. Late effects after ablative allogeneic stem cell transplantation for adolescent and young adult acute myeloid leukemia. *Blood Adv*. 2020; 4(6):983-992. DOI: 10.1182/bloodadvances.2019001126

3. Tichelli A, Bucher C, Rovó A, et al. Premature cardiovascular disease after allogeneic hematopoietic stem-cell transplantation. *Blood*. 2007;110(9):3463-71. DOI: 10.1182/blood-2006-10-054080