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General AML

Reduced relapse incidence with FLAMSA-RIC compared to busulfan/fludarabine conditioning for patients with acute myeloid leukemia

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Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially beneficial treatment option for patients with acute myeloid leukemia (AML). However, the optimal conditioning regimen for allo-HSCT remains debatable. Busulfan and fludarabine (BuFlu) is a commonly administered conditioning regimen as well as the FLAMSA (fludarabine + Ara-C + amsacrine chemotherapy) regimen with either cyclophosphamide and total body irradiation (FLAMSA-TBI) or cyclophosphamide and busulfan (FLAMSA-Bu).

In order to compare the results of patients with AML undergoing allo-HSCT in first- (CR1) or second complete remission (CR2) receiving either BuFlu or FLAMSA-RIC (FLAMSA-TBI or FLAMSA-Bu) conditioning, a group of researchers conducted a retrospective analysis on behalf of the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT). On 6 August 2018, the study was published ahead of print in the Biology of Blood and Marrow Transplantation.[2]

Data was collected from the EBMT registry. AML patients who underwent allo-HSCT in CR1 or CR2 between January 2005 and June 2016 in 134 centers were included in this study and received either BuFlu or FLAMSA conditioning. In total, 1,197 patients (median age = 58.8 years; range, 20.1–76) received BuFlu conditioning, while FLAMSA-TBI (median age = 47 years; range, 18.1–66.8) and FLAMSA-Bu (median age = 59.6 years; range, 19.6–74.4) were administered in 258 and 141 patients, respectively. The primary endpoint of the study was leukemia-free survival (LFS). Secondary endpoints included overall survival (OS), refined graft-versus-host disease-free/relapse-free survival (GRFS), neutrophil engraftment, acute graft-versus-host disease (aGvHD) and chronic GvHD (cGvHD), relapse incidence (RI), and non-relapse mortality (NRM).

Key findings in the BuFlu, FLAMSA-TBI, and FLAMSA-Bu groups:

- Median follow-up of survivors: 24.72 months
- Patients receiving BuFlu had a longer follow-up than patients treated with FLAMSA-TBI: 24.2 *vs* 40.3 months, $P < 0.001$
- 2-year LFS: 53.6% *vs* 61.6% *vs* 50.1%, respectively, $P = 0.03$
- RI: 30.3% *vs* 21.9% *vs* 23.1%, respectively, $P < 0.01$
- 2-year NRM: 16.1% *vs* 16.4% *vs* 26.7%, respectively, $P < 0.01$
- 2-year OS: 60% (95% CI, 56.9%–63.1%) *vs* 68.3% (95% CI, 62.3%–74.4%) *vs* 56.4% (95% CI, 46.8%–66.1%)
- 100-day cumulative incidence of grade II to IV and grade III to IV aGVHD after allo-HSCT: 22.9% (95% CI, 20.8%–25%) and 9.1% (95% CI, 7.7%–10.6%), respectively
- 100-day cumulative incidence of aGVHD II to IV in the BuFlu and the FLAMSA-TBI groups: 21.1% *vs* 26.9%, $P < 0.001$

- 2-year cumulative incidence of cGVHD rates: 34.7% (95% CI, 31.8% to 37.7%) *vs* 33.9% (95% CI, 27.6%–40.3%) *vs* 28% (95% CI, 19.8%–36.8%), (not significant), respectively
- Patients receiving FLAMSA-TBI compared with patients receiving BuFlu conditioning is significantly associated with lower RI: HR = 0.64 (95% CI, 0.42–0.98), $P = 0.04$
- 2-year LFS: 54.6% (95% CI, 52%–57.3%)
- Patients receiving FLAMSA-TBI compared with patients receiving BuFlu conditioning had improved LFS: HR = 0.72 (95% CI, 0.49–1.06), $P = 0.09$

In summary, this data indicates that BuFlu conditioning in comparison with FLAMSA-TBI conditioning show lower relapse incidence and superior leukemia-free survival. However, FLAMSA-TBI did not improve overall survival. Univariate analysis showed that FLAMSA-Bu compared with BuFlu led to increased non-relapse mortality rates. Additionally, no significant difference was found in any other of the study endpoints.

The research group stated that further prospective studies investigating the FLAMSA platform with other conditioning regimens are required, in order to establish risk factors, comorbidity scores and minimal residual disease status at the time of transplantation.

References

1. Heinicke T. *et al.* Reduced Relapse Incidence with FLAMSA-RIC Compared with Busulfan/Fludarabine for Acute Myelogenous Leukemia Patients in First or Second Complete Remission: A Study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2018 Aug 6. DOI: 10.1016/j.bbmt.2018.07.007. [Epub ahead of print].

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