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General AML

EBMT 2018 | Phase III study of HSCT in children with very high-risk AML

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The prospective phase III multicenter AML SCT-BFM 2007 study (NCT00606723, EudraCT: 2007-004517-34) was based on a hematopoietic stem cell transplantation (HSCT) consensus in children with very high risk acute myeloid leukemia (AML). The study aimed to prospectively generate a valid body of data on which additional transplantation techniques could be based. The results from this study were presented by Martin Saucer from the Medizinische Hochschule Hannover, Hannover, DE, on behalf of colleagues at the 44th Annual Meeting of the European Society for Blood and Marrow Transplantation (EBMT).

In this study, children with cytogenetic and molecular high-risk features in first complete remission (CR1) and CR2 after a first relapse underwent HSCT from a matched donor (MD) using a myeloablative conditioning (MAC) regimen consisting of Busulfan (age-adjusted i.v. dosing: 3.2 - 4,8 mg/kg BW on days 7–4), cyclophosphamide (60 mg/kg iv on days 3–2), and melphalan (140 mg/m^2 on day 1) termed BuCyMel.

Children with refractory primary disease or refractory relapse underwent HSCT using a cytoreductive regimen containing fludarabine (30 mg/m^2/d i.v.), amsacrine (100 mg/m^2/d i.v.) and cytarabine (2 g/m^2/d i.v.) all on days 12–9 (FLAMSA) immediately followed by a reduced intensity conditioning (RIC) consisting of 4 Gy TBI and Cyclophosphamide (60 (unrelated)/40 (related) mg/kg/d i.v.) on Days 4–3. After early taper of immunosuppression, increasing doses of prophylactic donor lymphocyte infusions (DLI) were given.

There were not enough patient numbers for randomization in this prospective phase III study, thus patients were risk stratified as follows:

- Patients in first relapse
  - Patients in CR2 with an available MD were transplanted with MAC- BuCyMel
  - There was no consensus for patients in CR2 without an available MD
  - Patients with poor response with an available MD were administered RIC FLAMSA
  - Patients with poor response without an available MD were administered RIC FLAMSA
- Patients with primarily refractory AML
  - Patients with an available MD were transplanted with RIC FLAMSA
  - Patients without an available MD were transplanted with MAC T-depleted Haplo
- Patients with *de novo* very high-risk AML in CR1
  - Patients with an available MD were transplanted with MAC- BuCyMel

- There was no consensus for patients without an available MD

Key findings in 97 children who underwent HSCT after conditioning with BuCyMel

- 3-year event-free survival (EFS) and overall survival (OS) were 62% and 73% respectively
- 3-year cumulative incidence of relapse (RI): 22%
  - Median time to relapse after allo-SCT: 8 months (range, 1–66)
- 3-year treatment-related mortality (TRM) rate: 15%
- 4-year EFS and OS in children (n = 25) < 12 years transplanted in CR1 were 84% and 92% respectively, *P* = 0.017
- 3-year TRM rate in children (n = 68) < 12 years: 9%
- 3-year TRM rate in children > 12 years: 31%

- Cumulative incidence of grade II–IV acute graft versus host disease (GvHD) and extended chronic GvHD were 28% and 7% respectively

Key findings in children who underwent HSCT with FLAMSA

- **In children (n = 35) with refractory AML**
  - 3-year EFS and OS were 46% and 51% respectively
  - 3-year CIR: 43%
  - 3-year TRM rate: 11%
- **In children (n = 19) with primarily refractory AML**
  - 3-year EFS: 53%
  - 3-year CIR: 42%
  - 3-year TRM rate: 5%
- **In children (n = 7) with relapsed refractory AML**
  - 3-year EFS: 29%
- Cumulative incidence of grade II–IV acute and extended chronic GvHD in patients with BU/CY/MEL were 23% and 6% respectively

The speaker concluded by stating that within this well-defined trial concept, myeloablative HSCT for AML in CR from a MD using BuCyMel for conditioning results in an EFS of 60% with a low TRM rate in children younger than 12 years at the time of transplantation. A similar approach in children older than 12 years is associated with a high TRM rate of 31%.

Additionally, “HSCT for poor responsive AML using FLAMSA-RIC plus prophylactic DLI results in an EFS of 46 percent and is extraordinarily well tolerated”.

References

1. Saucer M. *et al*. AML SCT-BFM 2007: Results of the prospective hematopoietic stem cell transplantation (HCT) trial of the Berlin-Frankfurt- Münster (BFM) study group for children with very high risk acute myeloid leukemia. Oral abstract #SS6-5. 2018 European Society for Blood and Marrow Transplantation (EBMT) Annual Meeting, Lisbon, PT.