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Long-term efficacy of reduced-intensity *versus* myeloablative conditioning before allogeneic HCT in patients with AML in CR1

Cynthia Umukoro | Apr 19, 2018

Previously published findings from a prospective phase III study (NCT00150878) which compared reduced-intensity fludarabine-based conditioning (RIC) regimen with a standard regimen in patients with acute myeloid leukemia (AML) in first complete remission (CR1) demonstrated that RIC results in a similar incidence of non-relapse mortality (NRM) and reduced toxic effects compared with myeloablative conditioning (MAC) without affecting survival outcomes.[1]

However, these results were focused on events occurring within the first 12 months after transplant and whether RIC before allogeneic hematopoietic stem cell transplantation (HSCT) increases the risk of late relapse compared to MAC regimen in patients with AML in CR1 is still unclear. Frederick Fasslrinner from University Hospital Carl Gustav Carus, Dresden, Germany, and colleagues carried out a retrospective 10-year follow-up of this phase III prospective trial. The results were published in Lancet Hematology.[2]

In this phase III study, a total of 195 AML patients in CR1 were randomly assigned to receive RIC (120 mg/m^2 fludarabine combined with four 2 Gy doses of total-body irradiation, n = 99) or MAC (six 2 Gy doses of total-body irradiation and 120 mg/kg cyclophosphamide, n = 95). The median follow-up time for surviving patients in this retrospective study was 9.9 years (IQR 8.5–11.4).

Key findings:

- 10-year cumulative incidence of relapse in the RIC and MAC group: 30% (95% CI 20–39) *vs* 30% (95% CI 21–40), Gray test *P* = 0.99
    - Median time to relapse in the RIC and MAC group were 5.0 (IQR 3.0–8.8) and 9.5 (IQR 4.5–20.5) months respectively
- 10-year cumulative incidence of NRM in the RIC and MAC group: 16% (95% CI 8–24) *vs* 26% (95% CI 17–36) respectively, sub-distribution hazard ratio (SHR) = 0.60, Gray test *P* = 0.10
    - Patients aged 41–60 years had significantly lower NRM after RIC compared to MAC: 13% (95% CI 5–22) *vs* 32% (95% CI 19–44), SHR = 0.44, *P* = 0.034
- 10-year disease-free survival (DFS) in the RIC and MAC group: 55% (95% CI 45–66) *vs* 43% (95% CI 34–55) respectively, HR = 0.76, *P* = 0.19
- 10-year overall survival (OS) in the RIC and MAC group: 60% (95% CI 50–70) *vs* 47% (95% CI 38–59) respectively, HR = 0.71, *P* = 0.10
- HCT-related death occurred in 15% (14/94) and 23% (21/90) of patients in the RIC and MAC group respectively, *P* = 0.67

- Secondary malignancies occurred in 6% (6/94) and 6% (5/90) of patients in the RIC and MAC group respectively, *P* = 1.00

In summary, long-term efficacy and late complications after allogeneic HSCT were similar between RIC and MAC. Furthermore, the findings of this study demonstrate that RIC is not associated with an increased risk of relapse when compared with MAC.

Key limitations of this study include its retrospective nature, reliance on medical records and limited sample size.

The authors concluded by stating that “given that the reduced-intensity conditioning group in the original trial was associated with lower early morbidity and toxicity, reduced-intensity conditioning with moderately reduced total-body irradiation doses could be the preferred conditioning strategy for patients with AML who are younger than 60 years and transplanted in CR1”.

References

1. Bornhäuser M. *et al.* Reduced-intensity conditioning versus standard conditioning before allogeneic haemopoietic cell transplantation in patients with acute myeloid leukaemia in first complete remission: a prospective, open-label randomised phase 3 trial. Lancet Oncol. 2012 Oct; 13(10): 1035–44. DOI: 10.1016/S1470-2045(12)70349-2. Epub 2012 Sep 7.
2. Fasslrinner F. *et al.* Long-term efficacy of reduced-intensity versus myeloablative conditioning before allogeneic haemopoietic cell transplantation in patients with acute myeloid leukaemia in first complete remission: retrospective follow-up of an open-label, randomised phase 3 trial. Lancet Haematol. 2018 Apr; 5(4): e161–e169. DOI: 10.1016/S2352-3026(18)30022-X. Epub 2018 Mar 14.