Long-term follow-up from MAvRIC trial

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The BMT CTN 0901 trial, also known as MAvRIC (NCT01339910), enrolled patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) and assigned them to receive myeloablative conditioning (MAC) or reduced-intensity conditioning (RIC) prior to allogeneic hematopoietic stem cell transplant (allo-HSCT).[1,2]

Study design

- Phase III, randomized, multicenter trial in patients with AML (n = 218) or MDS (n = 54) undergoing allo-HSCT[1,2]
- Patients were aged between 18 and 65 years and had < 5% marrow blasts (by morphology) prior to allo-HSCT[1,2]
- The study aimed to enroll 356 patients, however enrollment was stopped at 272 patients due to an imbalance in relapse rates[2]
- Conditioning regimens, by percentage of patients receiving each regimen[3]:
    - MAC:
        - Busulfan (16 mg/kg orally, or 12.8 mg/kg intravenously [IV]) plus fludarabine (120–180 mg/m^2): 64%
        - Busulfan (16 mg/kg orally, or 12.8 mg/kg IV) plus cyclophosphamide (120 mg/kg): 30%
        - Cyclophosphamide (120 mg/kg) and total body irradiation (12–14.2 Gy): 6%
    - RIC:

    - Fludarabine (120–180 mg/m^2) plus busulfan (≤ 8 mg/kg orally or 6.4 mg/kg IV): 81%
    - Fludarabine (120–180 mg/m^2) plus melphalan (≤150 mg/m^2): 19%
- Graft-*versus*-host disease prophylaxis (MAC *vs* RIC) [3]:
    - Methotrexate (MTX), 10–15 mg/m^2 on Day 1 and 5–10 mg/m^2 on Days 3, 6, and 11, administered with tacrolimus: 81.5% *vs* 81.8%
    - MTX (dosed as above) with cyclosporine (CSP): 2.2% for both arms
    - Tacrolimus (TAC) with sirolimus: 7.4% *vs* 8.8%
    - CSP with mycophenolate mofetil (MMF): 0.7% *vs* 0%
    - TAC with MMF: 5.9% *vs* 3.6%
    - Other: 2.2% *vs* 3.6%
- Median age: 55 years[2]
- Primary endpoint: overall survival (OS), 18-months from randomization[1,3]
- Secondary endpoints included relapse-free survival (RFS), disease relapse rate, treatment-related mortality, and neutrophil and platelet engraftment rate[1]

In an analysis of the MAvRIC study published in 2017 by Bart L. Scott and colleagues, MAC provided a statistically significant advantage in RFS at 18 months (67.8% *vs* 47.3%, $p < 0.01$). OS was found to be higher with MAC regimens (77.5% *vs* 67.6%), though not statistically significantly ($p = 0.07$). RIC led to a lower treatment-related mortality but also higher relapse rates.[3]

In February 2020, during the Transplantation and Cellular Therapy (TCT) Meetings of ASTCT and CIBMTR, Bart L. Scott, Fred Hutchinson Cancer Research Center, Seattle, US, presented long-term follow-up data from the trial, with a median follow-up of 50 months.[2]

[Given as MAC *vs* RIC throughout]

- 4-year overall survival (OS): 65% *vs* 49%, p = 0.02[2]
- Multivariate analysis for overall mortality[2]:
  - Hazard ratio (HR) for death (RIC *vs* MAC): 1.54 (95% CI, 1.07–2.20), p = 0.02
- Risk factors for mortality[2]:
  - High-risk disease, HR: 1.77
  - Age ≥ 50 years, HR: 2.20
- 4-year RFS: 58% *vs* 34%, p < 0.001[2]
  - HR for relapse (RIC *vs* MAC): 2.06 (95% CI, 1.48–2.85), p < 0.001
- Post-HCT relapse survival in patients with AML, 3 years after relapse: 24% *vs* 26%, p = 0.87[2]

Conclusion[2]

Long-term follow up shows MAC conditioning provides longer survival compared to RIC in younger, fit patients with AML or MDS undergoing allo-HSCT. This analysis confirms that the intensity of conditioning for allo-HSCT is important, with MAC being the optimal regimen for patients who are eligible for both options.

Read more about conditioning regimens in haploidentical transplants here and a comparison of treosulfan or busulfan plus fludarabine conditioning here.

References:

1. Clinicaltrials.gov. Reduced intensity regimen vs myeloablative regimen for myeloid leukemia or myelodysplastic syndrome (BMT CTN

0901).https://clinicaltrials.gov/ct2/show/NCT01339910. Updated 2018 May 30. [Accessed 2020 Mar 10]

2. Scott B.L. Long-term follow up of BMT CTN 0901, a randomized phase III trial comparing myeloablative (MAC) to reduced intensity conditioning (RIC) prior to hematopoietic cell transplantation (HCT) for acute myeloid leukemia (AML) or myelodysplasia (MDS) (MAvRIC Trial). Biol Blood Marrow Tr. 2020 Mar 01; 26(3):Supplement S11. DOI: 10.1016/j.bbmt.2019.12.075

3. Scott B.L. *et al.* Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. J Clin Onc. 2017 Apr 10; 35(11):1154–1161. DOI: 10.1200/JCO.2016.70.7091