GvHD Prophylaxis

Post-transplant cyclophosphamide as sole GvHD prophylaxis – a phase II study

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Biju George and colleagues from the Christian Medical College in Vellore, India, conducted a phase II trial investigating outcomes in patients who received post-transplant cyclophosphamide as the sole graft-versus-host disease prophylaxis after matched sibling transplant.

All patients in this study received peripheral stem cell product and were referred to transplant for a diagnosis of severe aplastic anemia. The transplant preparative regimen consisted of fludarbine for 6 days, cyclophosphamide for 2 days and a single day of total body irradiation. Prophylaxis cyclophosphamide was given at a dose of 50mg/kg/day on days +3 and +4 after transplant. The post-transplant cyclophosphamide prophylaxis was compared to 2 historical cohorts. Cohort 1 (MTX 15) used a prophylaxis regimen of cyclosporine and methotrexate, dosed at 15mg/m^2 once, followed by 3 doses of 10mg/m^2. Cohort 2 (MTX 10) used a prophylaxis regimen of 10mg/m^2 once, followed by 7mg/m^2 for 3 doses.

Key findings:

- Cyclophosphamide only cohort (PTCY)
  - N = 30
  - Median age = 29 years (16-49 years)
  - Median time from diagnosis to transplant = 5 months (2-108 months)
  - Received cyclosporine for >3 months prior to transplant = 30%
  - 3% received 2 post-transplant cyclophosphamide doses
  - 96% had complete donor engraftment at day +28
    - Median time to neutrophil engraftment = 16 days (12-21 days)
    - Median time to platelet engraftment = 15 days (10-32 days)
  - Grade II -IV aGVHD = 22.2%
  - Chronic GVHD = 22.7%
  - 6% did not require any further immunosuppression beyond cyclophosphamide
  - Three-year overall survival (OS) = 65.9%
  - Adverse events
    - Bacterial infection = 30%
    - Viral infection = 66.6%
    - CMV reactivation = 59.2%

    - Fungal infection = 13.3%

- PTCY compared to MTX 10 and MTX 15)
    - N = 90 patients total
        - PTCY = 30
        - MTX 10 = 30
        - MTX 15 = 30
    - aGVHD; PTCY = 22.2% vs MTX 10 = 53.8% vs MTX 15 = 37.1%, p = 0.056
    - cGVHD; PTCY = 22.7% vs MTX 10 = 76.2% vs MTX 15 = 63.6%, p = 0.001
    - Duration of immunosuppression; PTCY = 1.43 months vs MTX 10 = 36.6 months vs MTX 15 = 16.6 months, p = 0.000
    - Two-year OS; PTCY = 65.9% vs MTX 10 = 69.8% vs MTX 15 = 63.9%, p = 0.922
    - Two-year event-free survival; PTCY = 42% vs MTX 10 = 3.3% vs MTX 15 = 12.7%, p = 0.000
    - There were more viral infections in the PTCY group, but similar rates of bacterial and fungal infections across all groups

The results of this phase II study show encouraging results for single agent cyclophosphamide is this patient population. There was significantly less acute and chronic GVHD. The clinically relevant reduction in immunosuppression will be helpful to decrease the multitude of systemic adverse effects associated with immunosuppressant agents. The results also yielded a very meaningful improvement in 2-year survival, free of GVHD, rejection or death, even though there was no difference in overall survival. These represent favorable outcomes for patients with severe aplastic anemia.

References

1. *George B.et al*. Post-Transplant Cyclophosphamide as Sole Graft-versus-Host Disease Prophylaxis is Feasible in Patients Undergoing Peripheral Blood Stem Cell Transplantation for Severe Aplastic Anemia Using Matched Sibling Donors. Biology of Blood and Marrow Transplantation. 2018; 24(3): 494-500. DOI: 10.1016/j.bbmt.2017.10.034.