ALLOGENEIC STEM CELL TRANSPLANTATION IN PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

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Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired hematopoietic stem cell disorder, related to a somatic mutation in the phosphatidylinositol glycan class A (PIG-A), X-linked gene, leading to deficient expression of glycosyl (I) phosphatidylinositol–anchored proteins (GPI-APs). The disease is diagnosed with hemolytic anemia, marrow failure, or episodes of venous thrombosis events (TE). The clinical pleomorphic presentation of PNH has led to 2 recognize entities: one, predominantly hemolytic without overt marrow failure, is referred to as classical PNH1 and the other, with marrow failure, is often described as the aplastic anemia - PNH syndrome (AA-PNH) (2). Thromboses remain the major life-threatening complication in each disease subcategory (3,4).

Recent studies have focused on inhibiting the complement cascade, using Eculizumab, a humanized anti-C5 monoclonal antibody in patients with hemolysis (5,6). Eculizumab significantly reduces the risk of TE by inducing a significant and sustained decrease in the activation of both the plasma hemostatic system and the vascular endothelium (7), likely contributing to its protective effect on the risk of thromboembolism (8). Moreover, it has recently been suggested that Eculizumab improves survival (9). Patients with severe aplastic anemia (SAA) with or without a PNH clone are currently treated with either allogeneic stem cell transplantation (SCT) or immunosuppressive therapy (IST) depending on patient age and on the availability of a suitable Human Leukocyte Antigen (HLA)-matched hematopoietic stem cell donor (10).

The only curative treatment for PNH is SCT. In vitro and in vivo studies have shown that PNH cells can be eradicated following SCT (11). However, the risk for treatment-related mortality (TRM) after SCT is relatively high with graft-versus-host disease (GVHD) accounting for most of the TRM. There are limited number of single-center studies on SCT for PNH (12-21) (and reviewed in Parker (1) and Matos-Fernandez (22) and only one registry study involving more than 50 patients (23). The decision to perform an SCT in PNH has usually been deferred until disease progression, to recurrent, life-threatening thromboembolism, refractory or transfusion-dependent hemolytic anemia, or development of SAA (1,22).

Recently, the characteristics and overall survival (OS) of 211 patients transplanted for PNH in 83 EBMT centers from 1978 to 2007 were analyzed on behalf of the SAAWP of the EBMT (23). After a median follow-up of 5 years, the 5-year OS rate was 68%. Only TE indication for SCT was associated with worse outcome (p=0.03). Next, a comparison was done with a cohort of 402 non-transplanted PNH patients diagnosed between 1950 and 2005 in 92 French centers, according to complication occurrence [thromboembolism (TE), or aplastic anemia (AA)] using either an individual or a stratum matching procedure]. Twenty four pairs of transplanted and non-transplanted patients with TE were identified for the matched comparison, with worse OS for the transplanted patients [Hazard Ratio (HR) = 10.0 (95%CI, 1.3 - 78.1), p=0.007]. This was confirmed by the global matching procedure (p=0.03). Concerning AA, 30 pairs were identified for matched comparison. Not significantly worse OS was observed for transplanted patients [HR=4.0 (95%CI 0.9-18.9), p=0.06]. SCT is thus probably not a suitable treatment option for life-threatening TE in PNH nowadays. The results of this study as well as a global overview of SCT in PNH will be presented during the meeting.
References


15. Endo M, Beatty PG, Vreeke TM, Wittwer CT, Singh SP, Parker CJ. Syngeneic bone marrow transplantation without conditioning in a patient with paroxysmal nocturnal hemoglobinuria: in vivo evidence that the mutant stem cells have a survival advantage. Blood. 1998;88:742-750.


