Non-Myeloablative Stem Cell Transplantation for Congenital Immunodeficiencies

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Abstract

Allogeneic haematopoietic stem cell transplantation (HSCT) can be a highly successful treatment option for individuals with congenital immunodeficiency states. The strategy for HSCT is varied but in cases where there is preservation of residual T cell function, conditioning regimes have been used and have been based around a combination of busulphan and cyclophosphamide with or without serotherapy. In patients with coexisting organ damage this has resulted in significant morbidity and mortality. We have therefore used a low-intensity conditioning regime for transplantation in this group of immunodeficiency patients. Twenty-one patients with a variety of different immunodeficiencies were treated using the following conditioning regimes: (1) fludarabine/melphalan/ATG or Campath 1H \( (n=16) \), (2) fludarabine/cyclophosphamide/Campath 1H \( (n=1) \), (3) TBI/CyA/MMF \( (n=1) \), (4) fludarabine/melphalan/busulphan/ATG \( (n=3) \). In 13 cases matched \( (n=9) \) and 1 Ag mismatched \( (n=4) \) unrelated donors were used and in eight cases transplants from matched siblings \( (n=4) \), 1 Ag mismatched sibling \( (n=1) \), matched parent \( (n=1) \) and haploidentical parents \( (n=3) \) were performed. At a median follow-up of 13 months, 19 of 21 (90%) patients were still alive following the transplant procedure. Despite a T cell replete graft and the use of unrelated donor grafts in the majority of patients studied there was no evidence of significant organ disease. Immune reconstitution in terms of CD3⁺ and CD4⁺ T cell recovery and function was equivalent in comparison with a historical cohort. We believe that this low-intensity approach has significant implications for transplantation of individuals with immunodeficiency states with established organ disease.
Introduction

Allogeneic haematopoietic stem cell transplantation (HSCT) can be a highly successful treatment option for individuals with congenital immunodeficiency states. For the severe combined immunodeficiencies (SCIDs), the success following transplantation using genotypically matched sibling donors is greater than 90% (Fischer et al. 1990). Results from matched unrelated donor transplants are now also extremely encouraging and success rates of >70% 5-year survival have been reported (Vey et al. 1998). The optimal strategy for HSCT is varied. In true SCID (i.e. in patients with no evidence of T cell function) engraftment of donor cells from either matched or mismatched donors can be achieved without the need for a preparative conditioning regimen (Buckley et al. 1999). However, in patients with some degree of T cell function, a conditioning regime is required for stable engraftment and immune reconstitution. The beneficial effects of the conditioning are counterbalanced by increased short- and long-term toxicity. In particular, high treatment-related mortality is seen with conventionally conditioned HSCT in older children with combined immunodeficiency states who have established organ disease. In addition, late adverse effects such as growth retardation, infertility and secondary malignancy are difficult to justify in children with non-malignant disorders.

Conventional conditioning regimes for immunodeficiency have almost uniformly been based around the use of busulphan and cyclophosphamide with or without serotherapy. Busulphan is an effective myeloablative agent but exhibits significant toxicity against liver and lungs (Ringden et al. 1999). Recently, a number of groups have developed the use of less intensive conditioning regimes for the treatment of older or infirm patients with haematological malignancies (Storb et al. 1999a, b; Slavin et al. 1998). These non-myeloablative or “mini” transplants argue that complete myeloablation is not a prerequisite for donor haematopoietic engraftment. Instead, an immunosuppressive approach may result in mixed chimaerism of donor and recipient cells which exist in a state of host and graft tolerance. In studies on patients with haematological malignancies, mixed donor chimaeras were converted to full donor status using donor lymphocyte infusions in order to prevent disease relapse. A similar immunosuppressive approach has greater advantages for congenital immunodeficiency states where donor T cell engraftment alone should be sufficient to correct the disease phenotype. This strategy has been elegantly demonstrated in canine studies by the Seattle group, in which decreasing doses of total body irradiation (TBI) coupled with immunosuppression with cyclo-