Best Practice & Research Clinical Haematology
Vol. 21, No. 3, pp. 503–519, 2008
doi:10.1016/j.beha.2008.07.001
available online at http://www.sciencedirect.com

9

Post-transplant adoptive T-cell immunotherapy

Nicole A. Aqui* MD

Director of Apheresis Services, Hospital of the University of Pennsylvania
Assistant Professsor, Department of Pathology and Laboratory Medicine

Carl H. June MD

Director of Translational Research, Abramson Cancer Center
Professor, Department of Pathology and Laboratory Medicine
Abramson Family Cancer Research Institute and the Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA 19104–1416, USA

Immune reconstitution following haematopoietic stem cell transplantation (SCT) is an often slow and incomplete process that leads to increased risk of infection and malignant disease. Immunization in SCT is frequently unsuccessful due to the prolonged lymphopenia, especially of CD4 T cells, seen following transplant. The transfusion of T cells, also called 'adoptive T-cell therapy', has the potential to enhance anti-tumour and overall immunity, and augment vaccine efficacy in the post-transplant setting. Recent advances in tissue culture, cellular immunology and tumour biology are guiding new approaches to adoptive T-cell therapy. This chapter will discuss the challenges that face the field before adoptive T-cell therapy can be translated into routine clinical practice.

Key words: T cell; immune reconstitution; lymphopenia; haematopoietic stem cell transplantation; immunotherapy.

Stem cell transplantation (SCT) has a well-established role in the treatment of haematological malignancies. Both autologous and allogeneic SCT have demonstrated efficacy as therapy for patients with leukaemia, multiple myeloma and lymphoma. Additionally, the use of SCT is being explored for patients with autoimmune diseases. The post-transplant period is characterized by a prolonged period of immunodeficiency, leading to increased vulnerability to infection.[1–3] In one study, the majority of allograft recipients experienced

* Corresponding author. 272 John Morgan Building, 3620 Hamilton Walk, Philadelphia, PA 19104, USA. Tel.: +1 215 746 1195; Fax: +1 215 746 1100.
E-mail address: aqui@mail.med.upenn.edu (N.A. Aqui).

at least one late infection (>50 days to 2 years) after transplant.[4] Multivariate analysis showed that infection was the dominant factor associated with non-relapse mortality. In patients with chronic myeloid leukaemia, transplantation with a T-cell-depleted graft has been associated with an increased risk of relapse.[5] Several authors have reported a correlation between higher absolute CD4 and CD8 lymphocyte counts and improved disease-free and/or overall survival.[6–8] Even after lymphocyte numbers recover, lymphocyte function is often impaired.[9–11] These observations reinforce the importance of immune reconstitution in the overall effectiveness of transplantation.

Adoptive immunotherapy is the isolation, ex-vivo activation and infusion of antigen-specific or non-specific lymphocytes. Adoptive cellular therapy can be considered as a strategy aimed at tumour elimination through direct anti-neoplastic effects, or through indirect effects mediated by immunity directed against elements supporting tumour growth such as angiogenesis. Adoptive cellular therapy using autologous or allogeneic cell infusions may also have a role in replacing, repairing or enhancing the immune function damaged as a consequence of cytotoxic therapy. Analysis of the presently available clinical results suggests that, despite some disappointments, there is room for optimism that both adoptive immunotherapy and active immunotherapy (vaccination) may eventually become part of the therapeutic arsenal to prevent or combat cancer in a more efficient way. This chapter will describe the background, rationale, and current clinical use and experimental approach of adoptive cellular therapies to improve immune reconstitution in the setting of SCT for haematological neoplasms.

IMMUNODEFICIENCY FOLLOWING HAEMATOPOIETIC STEM CELL TRANSPLANTATION

In addition to compromising the ability of SCT patients to mount effective anti-tumour immune responses, post-transplant immune suppression clearly increases the risk for serious infections with varicella-zoster virus, cytomegalovirus and *Streptococcus pneumoniae*.[12,13] Early recovery of lymphocytes and lymphocyte function has been linked to improved survival following both auto- and allotransplantation.[6,14] In the immediate post-transplant period, lymphocyte restoration is achieved by expansion of mature T cells present in the graft, and not de-novo production from the thymus or bone marrow.[15–17] CD4+ T-cell regeneration occurs via a thymus-dependent mechanism, while CD8+ T-cell regeneration occurs via a thymus-independent pathway.[10,18] Therefore, after transplant, there is a prolonged deficiency of CD4+ T cells compared with CD8+ T cells, particularly in older patients, secondary to limited thymic regenerative capacity.[17,19] While younger patients eventually recover thymic output, the thymic deficiency seen following transplantation may not be fully reversible in older patients.[20,21]

The CD4+ T-cell deficiency noted after transplant is particularly significant as several studies have demonstrated the importance of these cells in the stimulation of CD8+ T cells and the enhancement of antibody production by B cells. CD8+ T cells that engage antigen in the absence of CD4+ T cells develop normally but do not proliferate well and do not persist, becoming so-called 'helpless T cells'.[22] This phenomenon may be responsible for the poor cytotoxic CD8+ T-cell responses seen in human immunodeficiency virus (HIV)[23], and could be operative in transplant patients. In addition to providing a critical stimulus for CD8+ T cells, CD4+ T cells are required for maximal antibody production.[24] The importance of CD4+ T cells has been demonstrated in humans where responses to immunization and severity of