

Adoptive transfer of CMV-specific T cells in transplantation

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Allogeneic stem cell (bone marrow) transplantation is utilized widely in the management of a range of malignant and non-malignant diseases of the haematopoietic system. The procedure involves the 'conditioning' of the patient through the use of chemotherapy and/or radiotherapy followed by the infusion of stem cells derived from an HLA-matched donor. Further immunosuppression is given in the post-transplant period in order to suppress the development of potentially fatal graft versus host disease.

Infection is a major complication of the post-transplant period and a range of bacterial and viral infections are encountered. A particular problem is the reactivation of latent herpes viruses such as cytomegalovirus (CMV) and Epstein-Barr Virus which are normally held in check through the action of the host immune response. CMV remains a significant cause of morbidity and mortality in such patients and is of particular consequence whenever T cell depletion of the stem cell product is incorporated.

Control of CMV has been improved through the development of early identification of viral reactivation and the use of anti-viral therapy. However, such an approach suppresses development of an effective CMV-specific immune response and late CMV disease is an increasing concern.

Adoptive transfer of CMV-specific T cells is an alternative method to control viral reactivation and has developed as a model of T cell therapy for a range of diseases. The initial methodology for transfer was to generate CMV-specific T cell lines and clones from a CMV-seropositive donor prior to infusion of large numbers ($>10^9$) of antigen-specific cells. However, this development is extremely demanding at a technical level and has not been widely adopted.

Recent years have demonstrated the unusually high magnitude of the CMV-specific immune response in CMV seropositive immunocompetent donors and this has allowed the introduction of novel mechanisms to transfer cellular immunity. In particular the use of HLA-peptide tetramers has led to the development of direct selection of CMV-specific T cells followed by immediate infusion into patients. In this situation small numbers of antigen-specific cells (typically around 1million) can lead to reconstitution of immunity. A similar approach can be taken with the cytokine secretion assay based on the selection of cells secreting interferon- γ in response to antigen stimulation. Randomised controlled trials are now in progress to determine the efficacy of these novel approaches and these will be discussed.