4 Application of T Cell Immunotherapy for Human Viral and Malignant Diseases


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4.1 Introduction

Improvements in our understanding of the molecular basis for T cell recognition of virus-infected cells and tumors, and of the signals involved in eliciting and maintaining a competent immune response has led to new efforts to bolster host T cell immunity in settings where deficient responses permit disease progression. The identification of viral antigens and antigens expressed by tumors has led to efforts to develop adoptive immunotherapy with T cell clones as a therapeutic approach to restore or augment host responses (Riddell and Greenberg 1995). The early results of clinical studies of T cell therapy for viral diseases have been encouraging and this approach is now being developed for the treatment of patients with leukemia that recurs after allogeneic bone marrow transplant (BMT) and patients with solid tumors.
4.2 Immunotherapy of Viral Diseases

4.2.1 Cytomegalovirus (CMV) Disease in Allogeneic BMT Recipients

CMV is a herpes virus that infects the majority of the population during childhood or adolescence and then persists in the host for life. In individuals with a normal immune system, persistent infection is controlled by the development and maintenance of host virus-specific immune responses. Patients with iatrogenic or acquired immunodeficiency frequently exhibit reactivation of CMV from latency or fail to limit a primary CMV infection and often develop visceral disease. Allogeneic BMT recipients who undergo complete ablation of their immune system prior to receiving a transplant of donor bone marrow or stem cells and then receive immunosuppressive drugs posttransplant to prevent graft versus host disease (GVHD), are at especially high risk for CMV interstitial pneumonia (CMV-IP) and enteritis. Before the advent of effective antiviral drug therapy, CMV-IP and enteritis occurred in 25% and 15% of CMV seropositive BMT recipients, respectively, and more than 50% of patients developing CMV-IP had a fatal outcome (Meyers et al. 1986). The use of the antiviral drug ganciclovir either as prophylaxis to prevent CMV reactivation or as preemptive therapy at the first sign of reactivation has reduced the incidence of CMV disease in the first 100 days after BMT but a significant number of patients still develop CMV disease following discontinuation of ganciclovir due to incomplete immunologic recovery (Goodrich et al. 1993; Boeckh et al. 1996). Thus, several studies have investigated the nature of the immunologic defects that permit progressive infection with a view toward developing interventions that would correct these defects.

4.2.1.1 Nature of the Immunologic Defects
The early period after allogeneic BMT is characterized by severe deficiencies of NK cells, antibody producing B cells, and CD4+ and CD8+ αβ T cell receptor-positive T lymphocytes. Individuals with congenital deficiencies of NK cells have an increased risk of severe and recurrent herpes virus infections and deficiencies of this subset may play a role in permitting the progression of CMV infection (Biron et al. 1989). However, NK activity appears to recover relatively early after BMT and